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2. Kirsner, J. B., and Sheffner, A. L.: Studies on Amino Acid Excretion in Man; VII. Effect of Various Protein Supplements in a Normal Man, Two Patients with Benign Gastric Ulcer and Two Patients with Chronic Ulcerative Colitis, J. Clin. Invest. *29*:828 (June) 1950.

3. Sappington, T. S., and Bockus, H. L.: Nitrogen Metabolism in Chronic Idiopathic Ulcerative Colitis and Its Therapeutic Significance, Ann. Int. Med. *31*:282 (Aug.) 1949.

4. Committee on Dietetics of the Mayo Clinic; Chronic Ulcerative Colitis: Dietary Program, in Mayo Clinic Diet Manual, ed. 2, Philadelphia, W. B. Saunders Company, 1954, pp. 59-62.

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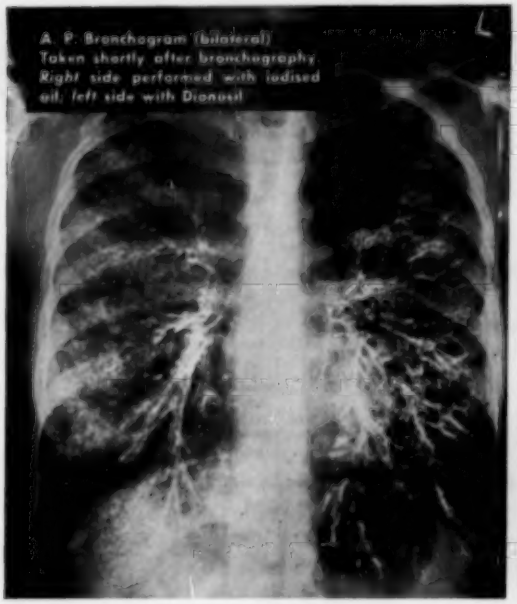
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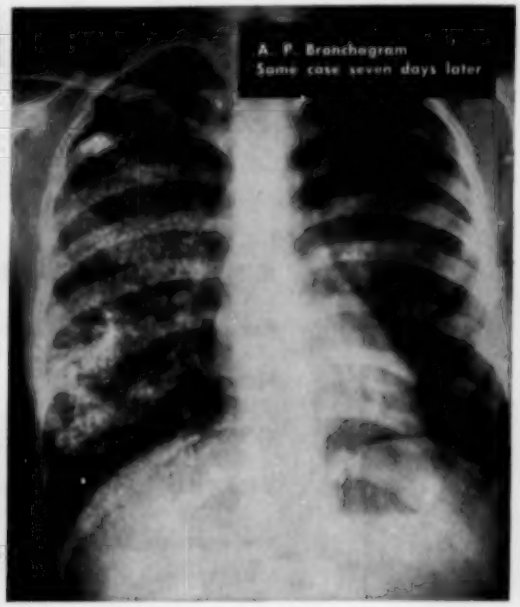

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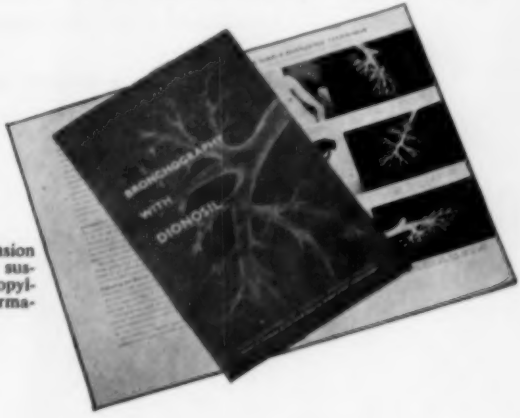

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ERRATUM

In Volume 70, No. 6, 1954, "Ambulaton of Patients with Pulmonary Tuberculosis Under Protection of Chemotherapy" by Sidney H. Dressler *et al.*, the third sentence in the second paragraph on page 1038 should be changed to read as follows:

As a consequence, it could be expected that this agent would *not* be effective as a short-term treatment of tuberculosis.

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SPECIAL EDITORIAL

The Closing of the Trudeau Sanatorium

An epoch in time is delineated by a significant change in orderly events. The change at the time may be interpreted as a sign of defeat or failure, and yet in the light of history it is shown to be a milestone of triumph in progress toward the achievement of a goal. The Trudeau Sanatorium is closed. How come? How does this event concern the National Tuberculosis Association?

The conception, the foundation, the development, the activities, the objectives, and the personages involved in both organizations have not only run parallel but are significantly intertwined.

The Trudeau Sanatorium was conceived of a need for a place to heal, share, and work by patients suffering from tuberculosis. With Dr. Edward L. Trudeau, as founder, the cradle of the Trudeau Sanatorium came into being as the "Little Red Cottage" in 1884. Later, as help was forthcoming from generous contributors, the "Adirondack Cottage Sanitarium" was incorporated in January, 1889.

The National Tuberculosis Association was conceived by a feeling of need to work, share, and develop means and ways to control and, if possible, eradicate tuberculosis. It was founded in June, 1904, with Dr. Edward L. Trudeau as its first president. At that time the national death rate from tuberculosis was approximately 200 per 100,000 population.

The Saranac Laboratory had its beginnings in a small corner wing of Dr. Trudeau's home and came to organized development as the Saranac Laboratory for the Study of Tuberculosis in 1894. The growth and maintenance of the sanatorium and laboratory were made possible by the establishment of an endowment fund.

A need for special training in tuberculosis nursing resulted in the establishment in 1912 of the Nurses Training School, specifically for ex-patient pupils.

The extension of the sanatorium movement resulted in the realization that a special postgraduate school for instruction in tuberculosis was most necessary. The logical site for this school was at Saranac Lake, with Dr. Trudeau as its founder. This project was established in 1914. The product of this school has included eminent chest specialists who later practiced and preached the "Trudeau Gospel" in all parts of the world.

Dr. Trudeau died on November 15, 1915. In 1917 the name of the institution was changed from Adirondack Cottage Sanitarium to Trudeau Sanatorium.

Soon after the passing of Dr. Trudeau, the friends of a lifetime joined in creating a special endowment to establish the Trudeau Foundation to support research and teaching programs. The income from this fund provides fellowships for study and research. As scientific research became more and more a part of the Sanatorium activity, additional funds in substantial amounts made possible the new Trudeau Laboratory built in 1923.

Thus, in evolution was developed a "tuberculosis university" which was the inspiration for the founding and development of many other sanatoriums and sent forth trained workers to guide the fight against tuberculosis into all parts of the world.

The activities of this "tuberculosis university" are shown by the citation of its accomplishments in one year. During 1952 it offered postgraduate courses in tuberculosis to thirty-eight doctors from the United States and abroad; trained twenty-five medical students as part of their medical school curriculum; gave eight weeks' experience in tuberculosis nursing to ninety-seven student nurses as part of their three-year basic nursing course; offered instruction to seven professional people who were themselves patients at Trudeau; participated in a refresher course in tuberculosis for general practitioners.

These accomplished objectives parallel the aims of the National Tuberculosis Association. Today the mortality rate for tuberculosis is approximately 12 per 100,000 of population.

To honor Dr. Trudeau's contribution to scientific research, the National Tuberculosis Association at the suggestion of its Committee on Medical Research founded a plan to award a medal, to be called the Trudeau Medal, each year to the individual who has meritoriously contributed to the cause, prevention, and treatment of tuberculosis. The first medal was awarded in 1926. Of the twenty-nine recipients of this honor, fourteen have had active training and participation in the activities of the Trudeau Sanatorium. The National Tuberculosis Association, through its Committee on Medical Research, has made grants for research annually to support meritorious work in the Trudeau Laboratory or Sanatorium. The National Tuberculosis Association has had fifty presidents, the first being Dr. Edward L. Trudeau, and sixteen of these have had active associations with the Trudeau Sanatorium. As a part of the celebration of fifty years of service for the Trudeau Sanatorium in 1935, the National Tuberculosis Association had its annual meeting at Saranac Lake. The medical section of the National Tuberculosis Association chose for its name "The American Trudeau Society."

The National Tuberculosis Association has contributed to the Trudeau Sanatorium, over the years of its own existence, moral and material support. It has in turn received significant help from the Trudeau Sanatorium in support of its objectives and in the training of persons to serve as its officers and in other valuable capacities. We have shared in the triumphs of the Trudeau Sanatorium, and we are interested in the future fate of its institutions. The doors of the Trudeau Sanatorium are closed, but the light of the "tuberculosis university," engendered in science and the humanities,—"To cure sometimes, to relieve often, to comfort always"—shines on.

JOHN H. SKAVLEM
President, National Tuberculosis Association

PULMONARY TUBERCULOSIS AFTER THE PROLONGED USE OF CHEMOTHERAPY[1, 2]

OSCAR AUERBACH

(Received for publication August 2, 1954)

INTRODUCTION

It has been the writer's impression that, since the advent of chemotherapy for the treatment of pulmonary tuberculosis, the anatomic findings are greatly different from those present in patients untreated with chemotherapy. The findings are so different, particularly in cases of long-term chemotherapy and in those in which treatment was begun soon after the onset of the disease, that such cases can be differentiated pathologically from those in which the disease had run a successful course without the benefit of the drugs.

This opinion is not shared, however, by the majority of writers who have expressed themselves on this subject. It is generally held that the drugs increase the rate of healing, but that the individual pathologic lesions are no different from those in the untreated cases.

Mahon (1) stated that there are no specific pathologic changes peculiar to tuberculous lesions which had been treated with streptomycin. He reported that the clearing of the perifocal reactions, the closure of cavities, and the encapsulation of caseous foci occurred with or without streptomycin. He further reported, however, that streptomycin increased the frequency of successful results and shortened the time required in the healing process. Silverthorne and Silverman (2) made similar observations and stated that no histologic finding was of sufficient individuality to be peculiar to the effects of the drug and that all could be demonstrated in lesions from untreated patients.

Recently Rich (3) stated that it is not possible to distinguish morphologically lesions which have been brought to the so-called "target point" with the aid of chemotherapy from lesions which have reached a similar point without chemotherapy.

As these views are different from the present writer's experience, it was believed that a comparison of the anatomic findings in patients who had received no chemotherapy with the findings in those who had received chemotherapy would be of interest. From these studies it soon became apparent that the single most important difference was the fate of the perifocal reaction in treated and untreated cases. The findings do verify the fact that the healing changes are accelerated under chemotherapy. Although the end results may in some ways appear to be the same, there are many qualitative and quantitative differences. The present paper represents an attempt to describe the changes in both types of cases and to explain the reasons for these differences.

[1] From the Laboratory Service, Veterans Administration Hospital, East Orange, New Jersey.

[2] Presented in part at the 54th annual meeting of the Canadian Tuberculosis Association, Saint John, New Brunswick, June 22–25, 1954.

The observations which will be presented are based on extensive study of the pathologic material of chronic pulmonary tuberculosis, both at autopsy and in surgical specimens. The material includes both treated and untreated lesions and is represented by more than 2,400 autopsy cases and more than 500 surgical specimens. All pathologic preparations were inflated with Kaiserling's solution, fixed, and cut, and multiple sections were taken from all significant areas. The microscopic tissues were examined with both hematoxylin and eosin as well as with van Gieson stains for elastic tissue. The treated patients, with relatively few exceptions, had a minimum of what is generally considered to be adequate antituberculous chemotherapy.

It is realized that, as in all biologic phenomena, there is a certain amount of variability. Nevertheless, it is believed that the following composite descriptions truly represent the over-all general trends and classifications which can be discerned from such a study.

Composite Descriptions of Changes in Tuberculous Lesions Attributed to Antimicrobial Therapy

The most striking changes in the tuberculous lesion which have been brought about by antimicrobial drugs have been the following: (*1*) rapid and extensive clearing of the perifocal reaction; (*2*) greatly decreased width of fibrous capsules around encapsulated necrotic foci; (*3*) decreased thickness of the cavity wall and of the overlying pleura; (*4*) decrease in pulmonary fibrosis and emphysema; (*5*) greatly decreased incidence in the development of pulmonary arterial aneurysms and consequent decrease in massive pulmonary hemorrhages; (*6*) difference in the mode of cavity healing; (*7*) more rapid healing of the tuberculous process.

Perifocal Reaction

As many of the differences between drug-treated and untreated lesions result from the altered development of the perifocal reaction, it might be well to review the characteristics of this process. The perifocal reaction was first described by Tendeloo (4) under the term of collateral inflammation and was also designated as circumfocal inflammation. Later the term perifocal inflammation was applied. The present writer prefers the term perifocal reaction, for there is a different response peripheral to the central core of inflammation. It is generally believed that the reaction is the result of the abnormal metabolic products which extend into the surrounding tissue from the necrotic focus.

The extent of the perifocal reaction is generally proportional to the extent of the disease which it surrounds. Sometimes, however, small tuberculous foci may result in wide areas of perifocal reaction while large foci may sometimes result in a small perifocal reaction.

The zone of perifocal reaction is found at the same time as the original area of tuberculous pneumonia. The pneumonic zone is firm and red-granular in the early stage and later is gray. Subsequently, yellow areas of necrosis develop within it. The perifocal reaction, which develops at the same time as the pneu-

monia, merges with it and is distinguished from it by being less firm and not granular. Sometimes the perifocal reaction has a gelatinous red or gray appearance and has been termed gelatinous pneumonia.

Microscopically, the perifocal reaction is characterized by an alveolar filling process composed of serum, erythrocytes, and alveolar phagocytes. Generally, the cellular components predominate in the alveoli near the tuberculous focus, while serum occupies most of the alveolar spaces in the more peripheral aspects. No neutrophils or fibrin are present, an important point of differentiation from the zone of acute inflammation which it surrounds.

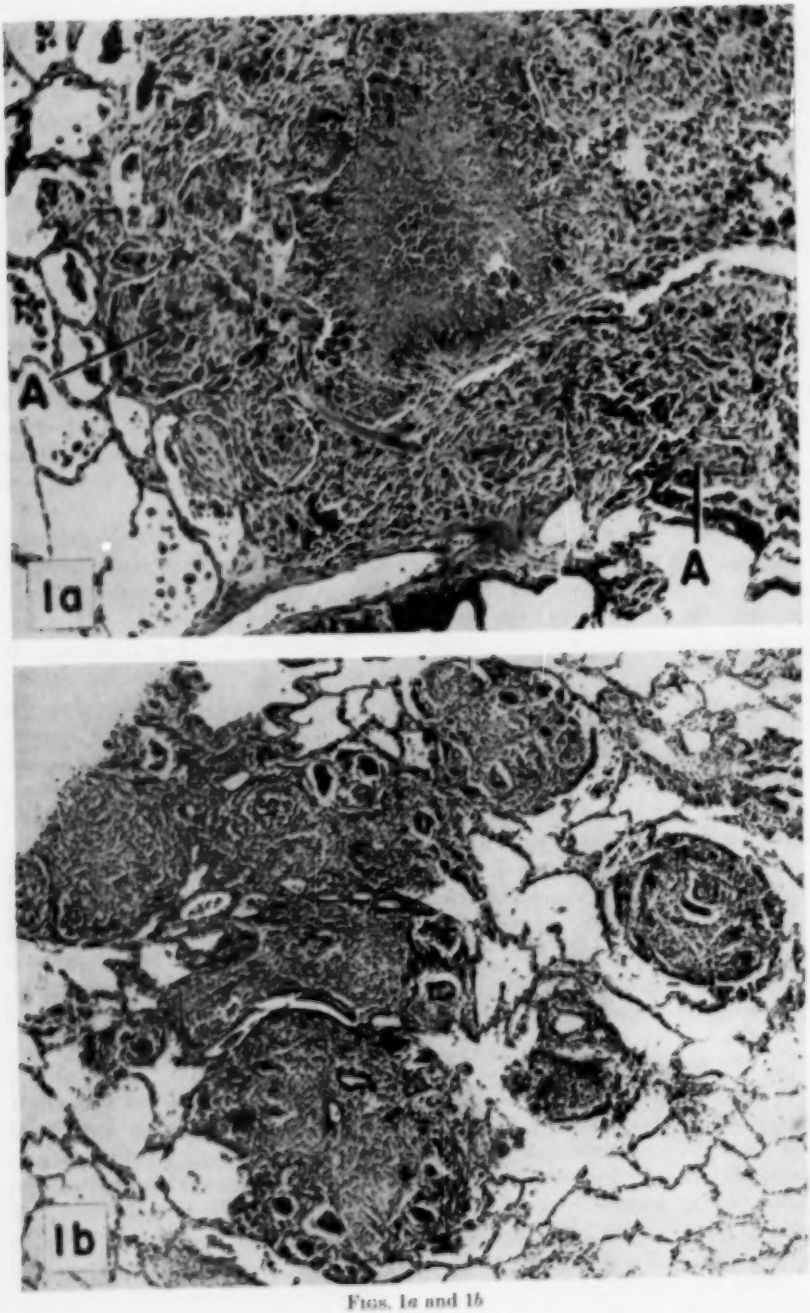
The ultimate fate of the perifocal reaction in lesions which are not treated by chemotherapeutic agents depends upon several factors. Generally, the clearing of this alveolar filling process occurs partially through the emptying of the contents through the draining bronchi and mainly by drainage through the lymphatic channels. Evacuation occurs chiefly in the peripheral portions where the serum predominates. Perifocal clearing occurs to its greatest extent when there is an isolated focus. Thus, even under ideal conditions, part of the alveolar filling process, generally the cellular portion near the focus, remains in the alveoli and is replaced by connective tissue.

Any interference with the routes of drainage will result in more of the perifocal reaction being trapped in the alveolar spaces and thus result in larger areas of eventual fibrosis. The two most important factors which interfere with the elimination of the perifocal reaction are the development of tuberculous foci in the neighboring regions and the institution of collapse therapy. The occurrence of adjoining tuberculous foci will result in a necrosis of the neighboring alveoli, bronchi, and lymphatics. Thus, the efferent bronchi and lymphatic channels through which the perifocal reaction might escape are blocked. Collapse therapy will also interfere with the avenues of escape by compression of the efferent bronchi and lymphatic channels. Thus, compression of the lung containing many tuberculous foci with surrounding perifocal reaction will result in wide areas of fibrosis and a great reduction in the lung volume.

It is the writer's impression that one of the most striking and beneficial effects of chemotherapy is the rapid and extensive clearing of the perifocal reaction. The prompt response is seen roentgenographically in the form of clearing of much of the shadow. This is particularly striking in the cases in which the process is acute and extensive. Following the clearing of the perifocal reaction the roentgenograms show a well-delimited tuberculous focus.

Fibrous Capsules Around Necrotic Foci

In the untreated lesion, when there is no blocking of neighboring bronchi or lymphatic channels, clearing of the perifocal reaction occurs in the peripheral aspects while organization occurs in the area immediately surrounding the tuberculous focus. The latter process occurs through the migration of fibroblasts, histiocytes, sometimes also newly formed capillaries, and with them formation of collagen fibrils (figure 1*a*). The alveolar filling process becomes continuous with the alveolar septa and, as the collagen fibrils increase, they fuse and compress the



FIGS. 1a and 1b

adjoining cellular elements until finally a loose zone of connective tissue results. Those alveoli in which no organization occurs are compressed by the surrounding connective tissue and are often lined by cuboidal cells. The resulting zone of loose connective tissue is directly continuous with the area of dense hyalinized connective tissue which results from the organization of the tuberculous granulation tissue which surrounds the solid necrotic focus. The inner zone of dense hyaline connective tissue has been designated as the specific portion of the capsule because of its origin from the specific tuberculous granulation tissue. The outer zone of loose connective tissue has been designated as a nonspecific portion of the capsule because it arose from the organized perifocal reaction. The latter zone is also characterized by the presence of coal pigment resulting from the interference with lymphatic drainage.

The lymphatic channels coursing through these areas are compressed by the connective tissue. Coal dust inhaled into the alveolar spaces is taken up by the alveolar phagocytes and carried by them through the lymphatic channels to the regional bronchial lymph nodes. The pigment-laden phagocytes cannot pass through the blocked lymphatic channels. They are forced through the walls of the vessels at this point as a result of the back pressure and are deposited in the surrounding connective tissue or are trapped locally. The phagocytes disintegrate and the pigment remains.

It is well recognized that the perifocal reaction clears to a much greater extent around a primary focus than around a post-primary focus. It has been emphasized that a distinguishing feature between these is the fact that the nonspecific capsule in the primary focus is thinner (5, 6). The areas of fibrosis around the necrotic zones are wider where the foci lie in groups, and often the areas of connective tissue form a common border to one another.

As has already been pointed out, following the institution of drug therapy, there is a rapid clearing of the shadows. This clearing represents the emptying of the alveolar contents in the perifocal reaction. This occurs immediately and is almost all-inclusive (figure 1*b*). Thus, the areas of tuberculous pneumonia undergoing necrosis are surrounded only by the zone of tuberculous granulation tissue. As a result of the early clearing of the perifocal reaction the capsules around the necrotic foci, when healing is complete, are thin and are composed of a narrow layer of hyalinized connective tissue. Generally, however, the institution of chemotherapy occurs after the tuberculous process has been present for some period of time. This would mean that some of the alveolar filling process of the

FIG. 1*a*. A 26-year-old white man with pulmonary tuberculosis for two and one-half years prior to his pneumonectomy (left). He received no chemotherapy prior to the operation. Photomicrograph shows an acinous focus with a necrotic center and a surrounding perifocal reaction in organization (*A*).

FIG. 1*b*. A 21-year-old white man with pulmonary tuberculosis for two years prior to his pneumonectomy (right). He received a course of chemotherapy (120 gm. of streptomycin, 1 gm. daily) following a spread of disease to his lower lobe. The lung was removed four and one-half months after the completion of chemotherapy. Photomicrograph shows the acinous foci in an advanced stage of healing with a complete absence of perifocal reaction. The foci are composed of epithelioid and giant cells with a large number of collagen fibrils.

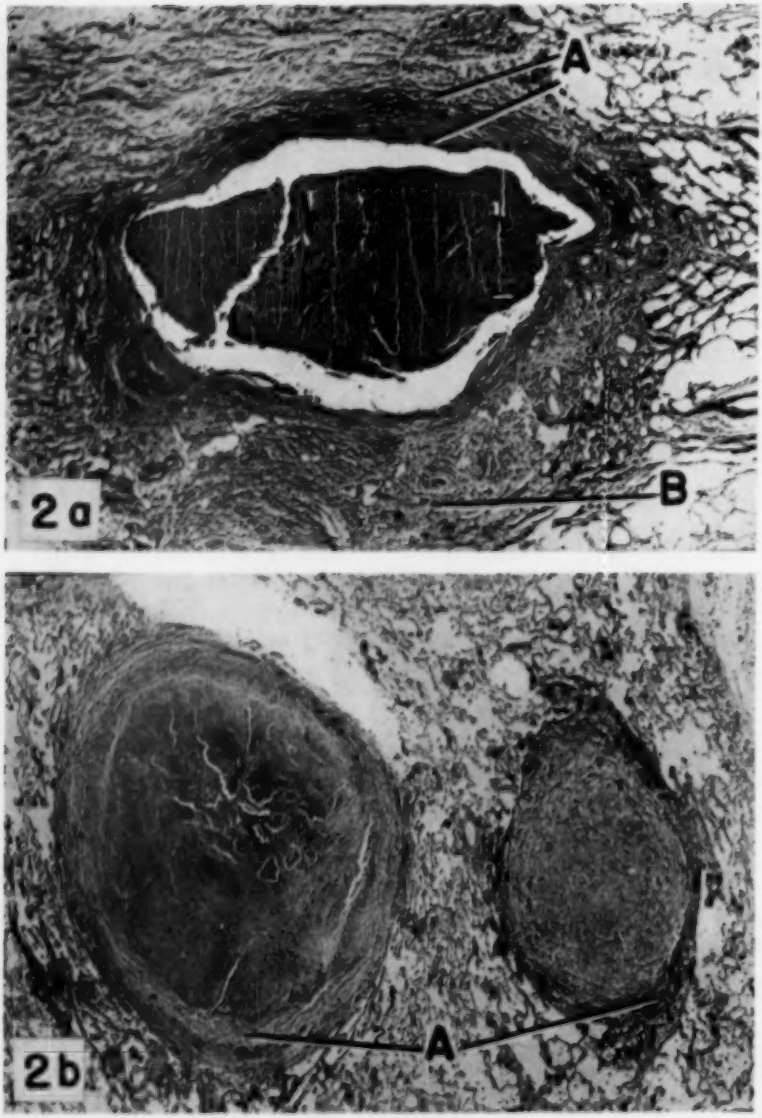


FIG. 2*a*. A 41-year-old white woman who died of uremia and amyloidosis fourteen years after the onset of pulmonary tuberculosis. No tubercle bacilli were recovered from her sputum for the last four years of her life. A healed cavity is present in the right upper lung field (figure 5*a*). Photomicrograph of an encapsulated caseous, calcified focus shows the necrotic center surrounded by a narrow band of hyalinized connective tissue (*A*) which in turn is encircled by a very wide zone of loose connective tissue (*B*) (organized perifocal reaction). This patient received no chemotherapy.

perifocal reaction has been converted into loose connective tissue. The administration of antimicrobials will not cause any resolution of the organizing or organized perifocal reaction. The extent of this zone will depend upon the time elapsed before the treatment with drugs was begun. It should be noted that recent necrotic foci without the benefit of chemotherapy are morphologically different from those chemotherapeutically treated.

The changes which result from the favorable effects of chemotherapy are permanent, and these healed tuberculous foci are much different from similar foci which heal without the benefit of the drugs (figures 2*a* and *b*).

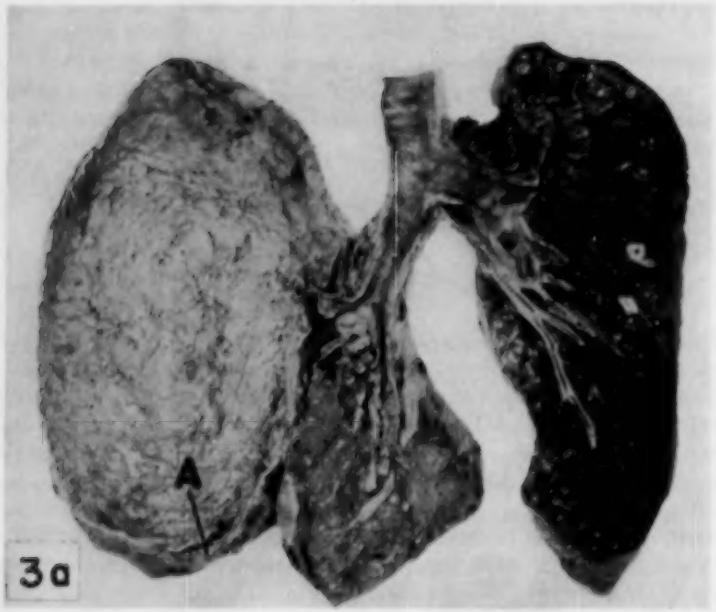
Decreased Thickness of the Cavity Wall and Decreased Thickness of Overlying Pleura

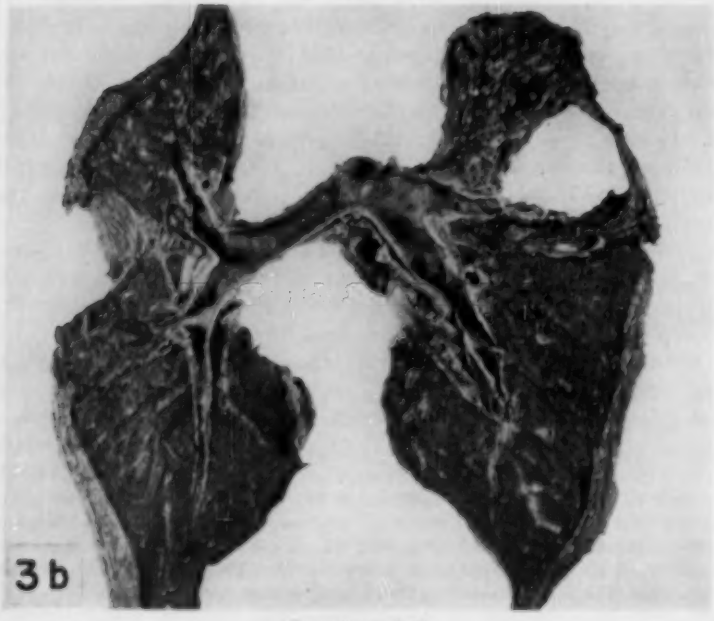
The organization of the perifocal reaction around the cavity forms the third layer of the wall and in part determines its thickness. The lining of the excavation is formed, in part, by a narrow rim of necrotic material and, in part, by a network of fibrin in which cells are enmeshed. The zone beyond this is composed of tuberculous granulation tissue rich in newly formed capillaries and cells and sparse in collagen fibrils in the early stage. The third layer results from the organization of the perifocal reaction.

As healing progresses, the collagen fibrils increase at the expense of the capillaries and cells. Thus, a newly formed cavity in which there has been only a small amount of organization of the perifocal reaction will have a thin wall and, with its progressive conversion into connective tissue, its thickness increases. Where progression of a cavity occurs, either through extension of necrotic foci into the lumen or progression from within, new areas of perifocal reaction develop around these new zones of activity. With the conversion of these new alveolar filling processes into connective tissue, the thickness of the cavity wall increases. The wall of a tuberculous cavity which has been present for a year or longer generally measures approximately 2 mm. in thickness, is gray or gray-black in appearance and, in its postero-lateral aspect, fuses with the overlying thickened pleura when it is in a position so that it is proximal to a pleural surface (figure 3*a*).

The pleural thickening is also the result of the perifocal reaction. Tuberculous cavities generally develop in a subpleural region several millimeters beneath the pleura. The perifocal reaction usually extends to involve the pleura and results in a localized collection of fluid and cells in this area. This is soon invaded by the elements of repair and is converted into connective tissue, with a resultant obliteration of the pleural space. If new cavities develop in this region or if the original cavity continually progresses, more of the pleural space will become

FIG. 2*b*. A 29-year-old white man whose pulmonary tuberculosis was detected twenty-two months prior to the removal of his right upper lobe. He received two courses of chemotherapy. One was begun within one month of the onset, and another prior to his operation. The first course was 90 gm. of streptomycin, the second was 42 gm. (each 1 gm. daily). Photomicrograph shows two encapsulated, necrotic foci. There are hyalinized connective tissue (specific) capsules (*A*) encircling the necrotic centers, but there are no outer zones of loose connective tissue (nonspecific) around them.





FIGS. 3a and 3b

obliterated. When the pleura overlies a cavity which has been present and actively progressive for a number of years, the combined thickness of the pleurae may reach a thickness of 1.5 cm. to 2.0 cm. and is densely adherent to the chest wall.

The clearing of the perifocal reaction around a tuberculous cavity following the institution of antimicrobial therapy results in a different thickness of its wall

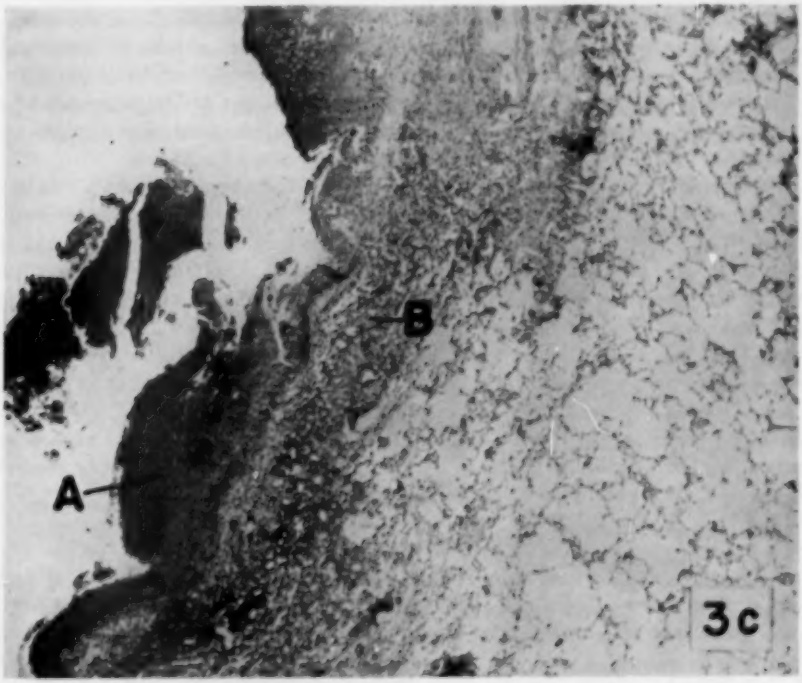


FIG. 3*a*. A 34-year-old Negro woman whose pulmonary tuberculosis was first discovered twenty-eight months prior to her death. She received no chemotherapy during her illness. A large cavity occupies the upper lobe of the left lung and fuses with the thickened pleura (*A*) in all aspects. The cavity is lined by a thick zone of necrotic material.

FIG. 3*b*. A 24-year-old white man who was admitted to the hospital seven months prior to his death in a semicomatose state, preceded by headaches for several days. A diagnosis of tuberculous meningitis was established. Roentgenographic examination of the chest showed a large cavity in the upper lobe of the right lung. The patient had raised brown sputum on occasions during the two months prior to admission. He was immediately begun on streptomycin therapy, 1 gm. daily, and intrathecal streptomycin, 50 mg. every other day. He received a total of 296 gm. of streptomycin up to the day of his death. The duration of his pulmonary tuberculosis was nine months. Coronal section of the lung shows a cavity with an extremely thin wall lying in the upper lobe of the right lung.

FIG. 3*c*. A photomicrograph of the cavity wall of figure 3*b* shows the inner wall composed of a necrotic layer (*A*). The layer of vascular granulation tissue beyond it (*B*) is of variable width. The empty alveolar spaces bordering the cavity, from which the perifocal reaction has been cleared as a result of the action of the drug, accounts for the thinness of the cavity.

as well as the thickness of the overlying pleura, when compared with similar untreated cases. The amount of fibrosis in these areas will naturally depend upon the age of the cavity at the time chemotherapy was instituted. Thus, if treatment were begun soon after its development, as a result of the clearing of the perifocal reaction and control of the organisms, the cavity wall would remain thin (figures 3*b* and *c*). If the tuberculosis advances and the process of healing under chemotherapy occurs with closure and inspissation of cavity contents, the wall will be thinner than one of similar age which closed without the benefit of the drugs. The former cavity wall will be composed of a fairly narrow zone of hyalinized connective tissue with little or no loose connective tissue beyond, while the latter will have a similar layer of hyalinized connective tissue but will be surrounded by a wider zone of loose connective tissue with variable amounts of coal pigment. The latter zone will often fuse with the thickened overlying pleura.

The writer has also had the opportunity to study cases in which "open" cavity healing has occurred during chemotherapy. In these lesions the necrotic contents have been completely evacuated and all that remains is a thin-walled cyst at the site of the former cavity. The dilemma of determining whether this is an emphysematous bleb is sometimes solved by serial sectioning of the tissue and finding small areas of tuberculous granulation tissue, which is conclusive proof of its being a healed cavity. Often there is a narrow intervening intact portion of lung parenchyma which lies between the cavity wall and the pleura. Pleural thickenings are in no way as extensive as in similar cases in which chemotherapy was not used. The institution of chemotherapy when cavities have been present for some period of time will not affect the outer wall of fibrosis or pleural fibrosis, but will prevent further thickening of the walls of the cavity.

Pulmonary Fibrosis and Emphysema

Pulmonary fibrosis and emphysema are frequent sequelae of healing and healed pulmonary tuberculosis. Fibrosis results in one of two ways, either from an organization of a tuberculous pneumonia or the organization of a perifocal reaction. In general, the larger the area of tuberculous pneumonia, the greater the chances are that it will undergo necrosis. Conversely, the smaller the focus, the greater the opportunity for organization to occur. Thus, many of the acinous nodose foci are converted into connective tissue. By far the larger amount of connective tissue results from the organization of the perifocal reaction. Wide areas of fibrosis result in a great contraction of the lung parenchyma and, thus, a great decrease in the lung volume. In many of the latter cases, it is common to find necrotic foci contiguous with one another and the outer fibrous capsules fused to one another.

Emphysema accompanies and generally parallels the extent of the pulmonary fibrosis. In the process of organization, both in the areas of tuberculous pneumonia and in the perifocal reaction, as the plugs, within the alveolar spaces which are adherent to the alveolar septa, are converted into connective tissue, there is a contraction of the lung parenchyma. As the pulmonary tissue contracts, there is then a stretching, thinning, and tearing of the alveolar septa in the regions imme-

diately around the fibrosis. This generally results in a weblike structure surrounding the zones of fibrosis and, in cases of healed pulmonary tuberculosis of wide extent, there are, in addition, bleb spaces varying from 5 mm. to 1 cm. in diameter.

Another important feature which results from chemotherapy is the general decrease in pulmonary fibrosis resulting from the cleared perifocal reaction, particularly in those cases in which, in addition to the cavities, there are many necrotic foci of varying size. As a result of this, necrotic foci having much thinner capsules which lie close to one another are now separated by intact lung parenchyma (figure 4).

As a result of the greatly lessened pulmonary fibrosis and contraction of the lung parenchyma, there is a much lesser degree of emphysema. Another feature

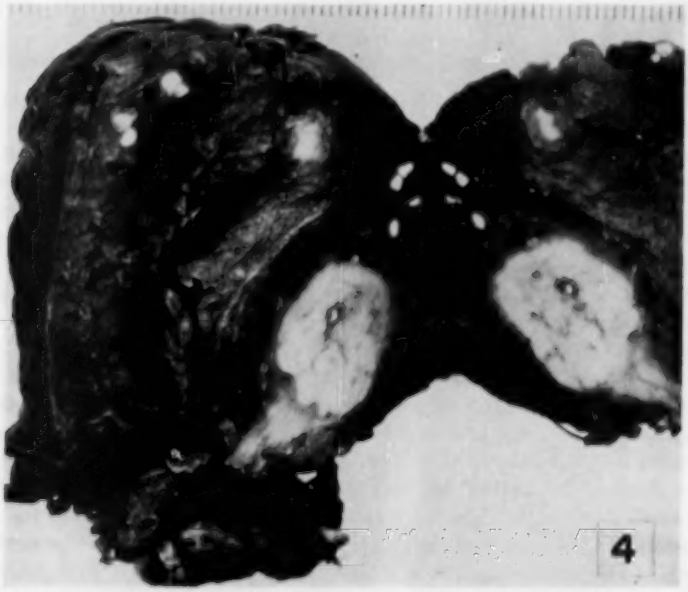


FIG. 4. A 25-year-old white man whose pulmonary tuberculosis was detected 32 months prior to a resection of the apico-posterior segment of the upper lobe of the left lung. Subsequently he received a sixty-day course of chemotherapy (streptomycin and PAS). One year before resection he had a hemoptysis. Subsequently there was an increase in the size of the large lesion in the lung. Streptomycin, 1 gm. twice weekly, and PAS, 12 gm. daily, were begun six months prior to resection and 300 mg. of isoniazid, twice weekly, were added two months later and continued up to the time of the resection. Tubercle bacilli were cultured from the sputum up to one month prior to resection. The resected specimen shows a large inspissated cavity in which acid-fast bacilli were demonstrable, both on microscopy and culture. The smaller necrotic foci in the surrounding lung tissue and the inspissated cavity are surrounded by thin capsules. The intervening lung tissue contains no areas of fibrosis. The overlying pleura is thin. Microscopically, a patent re-epithelized bronchus is found to communicate with the inspissated cavity.

of the greatly decreased fibrosis is that the lung volume is nowhere decreased to the extent which occurs in the absence of chemotherapy.

In general, it may be said that pulmonary fibrosis and emphysema are both greatly diminished in the lesions from drug-treated cases. This is much more evident when therapy has been instituted soon after the onset of pulmonary tuberculosis. When the disease has been present for months or years before the start of chemotherapy, the areas of pulmonary fibrosis and emphysema are unaffected by the drugs. In such cases, necrotic foci and cavities which develop just before the start of therapy or during such treatment can easily be distinguished from the older lesions which had healed before the institution of the drugs. The older foci and cavities will have wide zones of loose connective tissue in their outer aspects, while those showing the benefit of chemotherapy will have little or no loose connective tissue around the inner narrow zone of hyalinized connective tissue.

Pulmonary Hemorrhages as a Complication of Chronic Pulmonary Tuberculosis

Hemorrhage which results from the rupture of a pulmonary arterial aneurysm into the lumen of a cavity has been a frequent cause of death in chronic pulmonary tuberculosis in the era before chemotherapy (7, 8, 9). The development of an aneurysm results generally during the process of repair and is rarely observed in the more acute and rapidly progressive instances of pulmonary tuberculosis. The reason for this is the fact that branches of the pulmonary artery engulfed in the necrotic zones respond immediately by a fibrous thickening of the intima and obliteration of the lumen. Pulmonary arterial aneurysms generally result, not from these obliterated vessels traversing the cavity, but from vessels outside the cavity lumen.

It is not unusual to observe massive pulmonary hemorrhage in so-called "good chronics" with a persistent cavity which roentgenographically shows no evidence of progression for a long period of time. If a cavity persists, the processes of progression and repair keep pace with each other; thus, new areas of perifocal reaction develop in different regions around the periphery of the cavity. For an aneurysm to develop, new areas of perifocal reaction must develop in the region of a moderate-sized branch of the pulmonary artery, and the latter generally lies tangential to the cavity wall. As the alveolar filling process in this region is converted into loose connective tissue, it will, when it borders the outer wall of the artery, unite with it in one localized area. Serial sectioning of the structures at this site, after the fusing of both walls in this localized area, has shown that there

FIG. *5a*. The same patient as in figure *2a*, showing open healing in the upper lobe of the right lung without the benefit of chemotherapy. The cavity wall is thick, lined by a smooth gray surface, and fuses with the thickened overlying pleura. The remainder of the lung is replaced by connective tissue, greatly contracted with an obliteration of the fissures separating the lobes. The necrotic foci in the left lung (figure *2a*) are not visualized in this coronal section of the lungs.

FIG. *5b*. Photomicrograph of the cavity wall of figure *5a* shows it to be composed of a wide zone of dense connective tissue, from which all signs of tuberculosis have disappeared. The pleura (*A*) with which it fuses is also greatly thickened.

FIGS. 5a and 5b

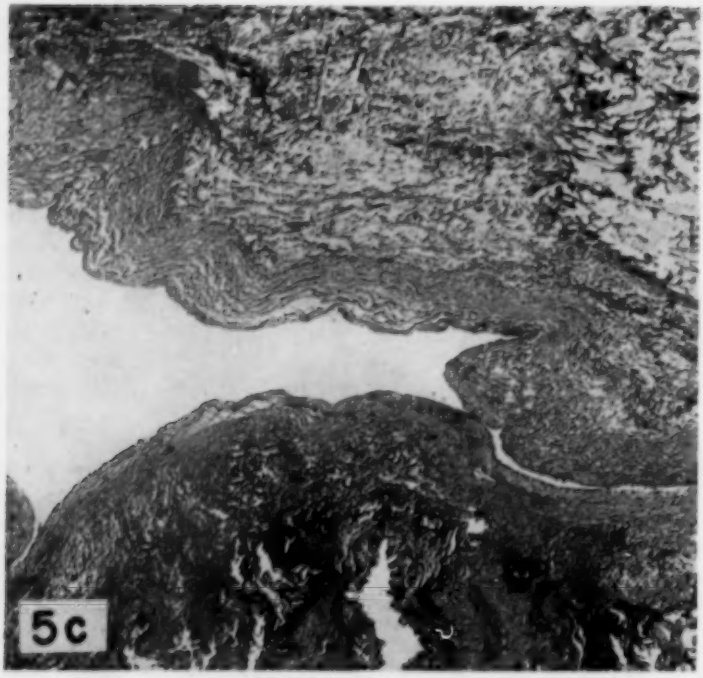


FIG. 5c. A 22-year-old white man whose pulmonary tuberculosis was detected thirteen months prior to a right upper lobectomy. Chest roentgenograms showed cavitation in the upper lobe of the right lung. He received eleven months of chemotherapy prior to his resection (streptomycin, 1 gm. three times weekly, and PAS, 12 gm. daily). The streptomycin dosage one month later was changed to 1 gm. twice weekly. Sputum cultures were positive for *M. tuberculosis* at the onset of his disease. Eleven sputum and gastric specimens taken in the last five months prior to operation were negative for *M. tuberculosis* on microscopy and culture. The cavity persisted in the chest roentgenograms.

The resected specimen showed a 3.5 by 2.0 by 3.0 cm. cavity lined by a smooth gray surface, to which one yellow necrotic fragment was attached. The wall and necrotic material were positive for tubercle bacilli on microscopy and culture.

Photomicrograph of the cavity wall shows it to be composed of a narrow zone of dense hyaline connective tissue in which all signs of specificity have disappeared. Branches of the bronchi communicate with the cavity.

is proliferation of the granulation tissue of the cavity wall which extends toward the intima of the blood vessel and destroys the elastic fibers of the artery in a circumscribed area. It is this weakened area which becomes the site of an aneurysmatic dilatation which bulges into the lumen of the cavity. When the aneurysm can no longer withstand the pressure in the lumen of the vessel, a rupture will occur.

One of the most dramatic occurrences which result from prolonged chemotherapy is the greatly decreased number of pulmonary hemorrhages. There are

several reasons for this phenomenon. As long as the tubercle bacilli remain susceptible to the drugs, the favorable effects are evident even in the presence of open cavities from which viable organisms are expectorated. Thus, in spite of the continued presence of an open cavity, the resolution of the perifocal reaction prevents the progressive development of pulmonary fibrosis in the outer rim of the cavity. At the same time, there is cessation of further cavity growth. As a result of this, the opportunity for encroachment on to the wall of a neighboring pulmonary artery by a cavity wall is greatly decreased.

The Difference in the Mode of Cavity Healing

Cavity healing may occur in the obliteration of the space, with either the inspissation of its contents or replacement by a radial scar. This has been termed closed healing, and the former is a much more frequent end result than the latter.

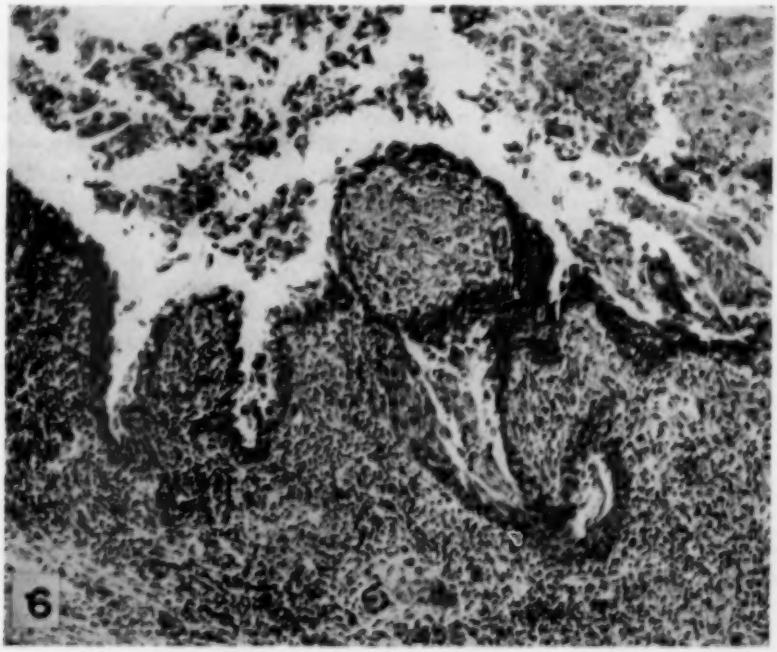


FIG. 6. Photomicrograph of the bronchocavitary junction from the lung of a 22-year-old white man whose pulmonary tuberculosis was discovered eight months before the resection of the apico-posterior section of the upper lobe of the left lung. He received streptomycin, 1 gm. twice weekly, and PAS, 12 gm. daily, for the last four months prior to surgery. Sputum which had previously been positive on microscopy and culture was negative for tubercle bacilli for two months prior to the excisional surgery. At the time of resection, a 4.5 cm. by 2.5 cm. by 2.5 cm. inspissated cavity was found in the excised specimen. Branches of the bronchus opened widely into the cavity.

Photomicrograph of the bronchocavitary junction shows a wide layer of squamous epithelium lying on a zone of vascular granulation tissue.

Another form is open healing in which the cavity remains open and the wall is composed of dense connective tissue from which all elements of specificity have disappeared. Occasionally it is partially or completely lined by a layer of epithelium, usually squamous in character.

In the era before chemotherapy, closed healing was by far the more frequent type, observed especially with the aid of collapse therapy. Closure of the cavity occurred as a result of the apposition of the granulating surfaces of the ulcerated bronchus at the bronchocavitary junction. Following this closure, air is absorbed from the lumen of the cavity and the cavity wall contracts quite rapidly. As most cavities contain large necrotic masses within the lumen and along the cavity wall, at the time of closure these become inspissated and form the center of the closed cavity. Occasionally, only small necrotic particles are present in the cavity at the time of closure. The end-result in these cases is a radial scar within which a small necrotic focus may be found occasionally.

"Open" healing with or without epithelization in patients who have received no antimicrobial therapy is extremely rare. In the few cases observed, the necrotic contents within the lumen of the cavity are evacuated and the necrotic lining is either desquamated or converted into dense hyalinized connective tissue. The surface lining the cavity is smooth and gray. The wall is extremely wide, fuses with the overlying thickened pleura (figure 5*a*), and is composed of connective tissue in which all signs of specificity have disappeared (figure 5*b*). The bronchi opening into these cavities are widely patent, lined by intact columnar epithelium, and show no evidence of tuberculosis. An increase of connective tissue and lymphocytic collections in the wall near the bronchocavitary junction is believed to represent the end result of a previous inflammatory process at this site. The thick cavity walls in the writer's cases are explained by the long duration of progressive disease before the complete shedding of tubercle bacilli from the cavity.

There are definite and striking qualitative differences brought about by chemo-

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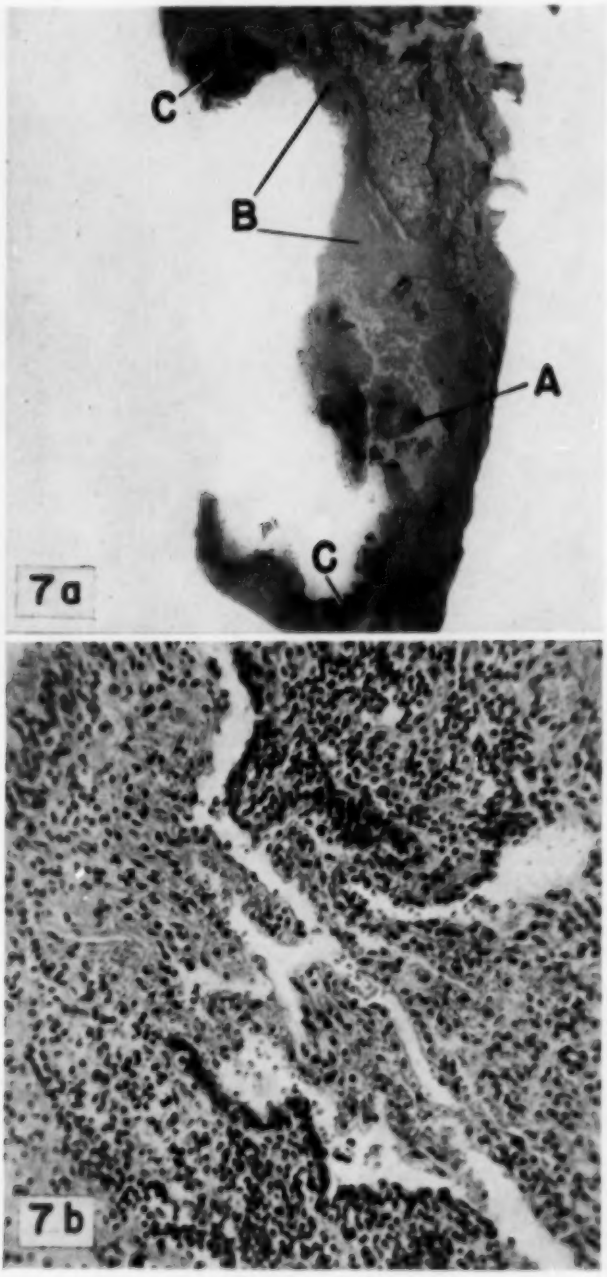
FIG. 7*a*. A 28-year-old white man was admitted because of a pulmonary infiltration on a routine survey. Chest roentgenograms taken three years previously did not show this lesion. He was completely asymptomatic, and all diagnostic studies, including sputum culture for tubercle bacilli, were negative. Because of the anterior location of the density and the possibility that it might represent a neoplasm, it was excised. He received no chemotherapy prior to his operation.

A 4 cm. by 3 cm. by 3 cm. inspissated cavity corresponding to the pulmonary infiltration was found in the resected specimen. The necrotic contents could easily be evacuated. No bronchial communication with the cavity could be demonstrated.

Photomicrograph of the cavity wall and surrounding tissue with much inspissated necrotic material absent. Some necrotic fragments (*A*) are present in the lumen. The inner wall is lined by a variably wide necrotic zone (*B*) containing calcium salts (*C*).

FIG. 7*b*. Serial sections of the cavity wall and the adjoining bronchi were performed to determine the relationship of the bronchi to the cavity. A series of these sections showed the reason for the lack of communication to lie in an obliteration of the bronchial lumen. Photomicrograph of one of these sections shows the lumen of the bronchus to be occluded by a "plug" of tuberculous granulation tissue which is continuous with the wall of the bronchus on each side. Intact columnar epithelium of the bronchial wall not involved by the "plug" is unaffected by the process. The patient had received no chemotherapy.



FIGS. 7a and 7b

FIG. 7*c*. A 49-year-old white man whose pulmonary tuberculosis was discovered seven months before right upper lobectomy and segmental resection of the apical segment of the lower lobe of the right lung. Ten years prior to this he had recurrent attacks of pleurisy. A chest roentgenogram showed a cavity in the right upper lobe. The sputum was positive for tubercle bacilli. Streptomycin, 1 gm. daily, and PAS, 12 gm. daily, were given for four months prior to resection. Sputum and gastric contents remained negative for tubercle bacilli for two months prior to resection. The cavity, although decreased in size, was still visible on the roentgenograms.

Photomicrograph of the cavity from the upper lobe shows the lumen to be partially filled with necrotic material. The bronchocavitary junction is lined by epithelium (*A*) which extends into the cavity for some distance (A^1).

therapy. The two most important changes following chemotherapy are the difference in cavity closure and the increased number of cases of "open" healing of cavities.

Cavity inspissation under chemotherapy occurs with re-epithelization of the bronchus at the bronchocavitary junction. Re-epithelization disrupts the check-valve mechanism which existed at the bronchocavitary junction as a result of the ulcerated bronchus. As a result of this, the distension of the cavity no longer occurs. Contraction of the granulation tissue of the cavity is now possible with a decrease in the size of the lumen and inspissation of the necrotic contents. The

epithelium in many instances extends around the inner wall of the cavity for variable distances. Re-epithelization prevents obliteration of the bronchial lumen at this site and prevents permanent closure of the cavity (figure 6).

When the inspissated cavity following chemotherapy is compared with the cavity healed without the benefit of drugs, it is found that in the former the bronchus is patent (figure 7*c*), while in the latter no bronchial communication can be demonstrated (figures 7*a* and *b*). As a result of this, greater drainage of the necrotic fragments from the lumen of the cavity is possible. The writer has observed an increased number of instances of "open" healing since prolonged chemotherapy and believes that this is attributable in great part to the re-epithelization of the bronchus at the bronchocavitary junction.

Another factor which, it is believed, contributes to the greater incidence of open healing now seen is that late liquefaction may occur in the inspissated cavities. This process occurs by way of the open bronchus where mucin intermingled with neutrophils result in a liquefaction of the necrotic contents. After evacuation of the liquefied contents, an open cavity now exists at the site of a previous closed cavity. The reappearance on the roentgenogram of a cavity which had previously been closed is being observed with greater frequency in cases under prolonged chemotherapy. The cavity wall in such cases is generally thin and is composed of dense connective tissue, with a complete disappearance of all signs of specificity for tuberculosis (*see* figure 5*c*). Such healed cavities, because of their thin walls, may be mistaken for lung cysts or emphysematous blebs. Bronchi open widely into these cavities and are completely intact.

More Rapid Healing of Tuberculous Process

There is almost complete unanimity among observers that healing of tuberculous processes is more rapid as a result of chemotherapy. This finding is a relative one since the rate of healing without antimicrobials is not constant. The comparison must be made in cases in which the age of tuberculous cavities and foci is approximately the same. This is especially striking when drug therapy is instituted soon after the development of the tuberculous process. Evidence of the more rapid healing is seen in the accelerated development of collagen fibrils and the corresponding decrease in cells and capillaries of the granulation tissue around the solid necrotic foci and the walls of tuberculous cavities.

SUMMARY

There are definite changes which occur in cases of chronic pulmonary tuberculosis after chemotherapy which are permanent and different from those in untreated cases. The degree of difference depends upon the time interval between the onset of tuberculous infection and initiation of chemotherapy and also upon the duration of therapy.

The following differences are observed after chemotherapy and are believed to be secondary to rapid clearing of the perifocal reaction by specific drugs: (a) the capsules around necrotic foci are thinner; (b) the walls of cavities are thinner;

as is the pleura overlying these cavities; (c) there is decrease in pulmonary fibrosis and emphysema; (d) there is decrease in the number of aneurysms in the cavity and the incidence of pulmonary hemorrhages.

Cavity closure occurs with a patent and re-epithelized draining bronchus. "Open" cavity healing occurs with greater frequency, especially after prolonged chemotherapy.

SUMARIO

La Tuberculosis Pulmonar Consecutivamente al Uso Prolongado de la Quimioterapia

En los casos de tuberculosis pulmonar crónica ocurren, después de la quimioterapia, alteraciones bien definidas que son permanentes y distintas de las observadas en casos no tratados; la intensidad de la diferencia depende del tiempo transcurrido entre la iniciación de la infección tuberculosa y la iniciación de la quimioterapia, y además de la duración de la terapéutica.

Obsérvanse las siguientes diferencias después de la quimioterapia y son secundarias al rápido despejo de la reacción perifocal por drogas específicas: (*a*) las cápsulas son más delgadas alrededor de focos esfacelados; (*b*) las paredes de las cavernas son más delgadas e igualmente la pleura sobrepuesta a ellas; (*c*) hay disminución de la fibrosis y del enfisema pulmonares; (*d*) hay disminución del número de aneurismas en la caverna y de la incidencia de hemorragias pulmonares.

Ocurre clausura de las cavernas cuando existe un bronquio de drenaje permeable y re-epitelializado. La cicatrización de las cavernas "abiertas" es más frecuente, sobre todo después de la quimioterapia prolongada.

RESUME

Tuberculose pulmonaire après emploi prolongé de la chimiothérapie

Il existe des modifications particulières qui se manifestent dans les cas de tuberculose pulmonaire chronique à la suite de la chimiothérapie; elles sont permanentes et différentes de celles des cas non traités. Le degré de ces différences dépend de la durée de l'intervalle entre le début de l'infection tuberculeuse et l'institauration de la chimiothérapie ainsi que de la durée du traitement.

Les modifications qui s'observent après la chimiothérapie, et secondaires à la guérison rapide de la réaction périfocale par les drogues spécifiques, sont les suivantes: a) les capsules qui entourent le foyer nécrotique sont plus minces; b) les parois des cavernes sont amincies ainsi que la plèvre recouvrant ces cavernes; c) il y a une réduction de la sclérose pulmonaire et de l'emphysème; d) il y a une réduction du nombre d'anévrismes dans l'excavation et de l'incidence des hémorragies pulmonaires.

L'oblitération de la caverne se produit avec une bronche de drainage perméable et réépithélialisée. La cicatrisation de la caverne "ouverte" se produit avec une fréquence plus grande, surtout après une chimiothérapie prolongée.

Acknowledgment

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MODIFICATIONS OF TUBERCULOUS LESIONS IN PATIENTS TREATED WITH ISONIAZID[1]

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INTRODUCTION

Antimicrobial drugs for the treatment of pulmonary tuberculosis have not only altered the clinical course and prognosis of the disease but have also modified its histologic patterns. Before streptomycin was brought into use, the routine treatment methods did not have direct influence on the causative agent of tuberculosis. Therapeutic benefits consisted essentially in improvement of the defense mechanisms of affected tissues. The new drugs introduced another element: the bacilli themselves suffer the effect of the drug which reduces their *number* and, perhaps as far as isoniazid is concerned, their *virulence* (1, 2). This will necessarily reflect on the histologic picture. The present writers have had no personal experience with the modifications of tuberculous lesions caused by streptomycin. Examination of the existing literature on the subject (3–11) reveals that there are no specific pathologic changes related to tuberculous lesions treated with this drug and that it merely enhances healing. Evidence for the effect on healing includes the intensive and often massive fibrosis of miliary foci, frequent presence of small scars of nonspecific character in the pulmonary parenchyma, and vigorous encapsulation of more voluminous necrotic foci. The perifocal reaction is usually absent. Areas of the lung which presumably once were the site of tuberculous lesions reveal foci of lymphocytic infiltration, fibrous endarteritis, and areas of chronic pneumonia with an unusual number of giant cells.

In contrast, with isoniazid, the present writers in agreement with Denst (12) have encountered some histologic features peculiar to surgical specimens from patients treated with this drug. Although most of the patients had received streptomycin or para-aminosalicylic acid (PAS) in addition to isoniazid, it appears that the characteristic changes noted resulted from the action of isoniazid. There are two reasons to support this conclusion. The characteristic tissue changes have never been encountered in patients treated with streptomycin and PAS alone. The changes have been pronounced in some patients in whom it was possible to perform pulmonary resection only after substantial improvement of the roentgenographic picture following months of treatment solely with isoniazid.

MATERIALS AND METHODS

A study was made of 56 surgical specimens from the surgical service of the Hospital-Sanatorio Santa Maria. The material included specimens from 16 pneumonectomies, 33 lobectomies, 5 lobectomies associated with segmental resections, one bilobectomy, and one simple segmental resection. Gross anatomic changes were recorded in schematic designs after the pieces had been fixed in formalin and cut in slices parallel to the hilum. For histologic study, the lesions considered to be the most interesting in each case were chosen:

[1] From the Hospital-Sanatorio Santa Maria and Conjunto Sanatorial de Curicica, Rio de Janeiro, Brazil.

cavity walls, draining bronchi, foci of regressive or residual aspect, calcified nodules, et cetera. The following staining techniques were used: hematoxylin and eosin, Gömöri trichromic, and the Mallory and Perdrau stains.

OBSERVATIONS

Some of the following anatomic and histopathologic changes have been found after the use of streptomycin according to the available literature, and may be interpreted as a result of acceleration of the known healing processes. Other changes noted, however, seem to be characteristic of the action of isoniazid.

Septal and pericavitary hyperemia, alveolar hemorrhage: The most impressive feature, and one believed to be peculiar to the effect of isoniazid, was the hyperemia provoked around caverns and encapsulated foci or in alveolar septa. The hyperemia was commonly accompanied by the invasion of masses of red globules into the alveoli. Simple inspection often uncovered signs of this phenomenon in the form of a thin perifocal or pericavitary hemorrhagic halo and rosy coloring of necrotic debris which frequently assumed a gelatinous and translucid appearance. This presumably represents an explanation for the bloody sputum so often observed in patients treated with isoniazid. In the experience of the writers, this complication is not serious and is rarely followed by severe hemoptyses.

Atypical location, unusual number, and pleomorphism of giant cells: The number of giant cells seen was often unusually large, such as has been described in patients treated exclusively with streptomycin. One phenomenon noted which appeared to be attributable to the peculiar effect of isoniazid was the atypical location of the numerous giant cells, as pointed out by Denst. The present writers could find these giant cells naked within the alveoli or surrounded by mucus in the interior of small bronchi, ready to be expectorated. At times the giant cells were found imprisoned within dense masses of collagenic tissue. Moreover, their pleomorphism was striking, and sometimes they were very strangely shaped.

Exuberant collagenous formation: Exuberant collagenous formation was noted in patients treated exclusively with streptomycin. This phenomenon seemed to be more pronounced, however, in the tissues from patients treated with isoniazid. Zones of massive fibrosis in which collagenous bundles were of uncommon thickness were frequently observed. In the interior of these zones there were frequently seen masses of lymphocytes, isolated giant cells, or groups of polymorphonuclears discharged from small vessels. This probably represented collagen formation at an accelerated rhythm which encapsulated the necrotic foci and caused rapid carnification of areas of macrophagic or fibrino-macrophagic alveolitis.

Bronchiolar hyperplasia and epithelial proliferation: Another very frequent finding was hyperplasia of the bronchioles, exuberant proliferation of the bronchiolar epithelium, sometimes of papillomatous appearance, and lining of the alveolar spaces with an epitheliform cellular layer. In agreement with Policard (13), the present writers believe that this histologic change is not caused by an epithelium of endodermic origin, pre-existent in the normal alveolus, but by mesenchymal cells disposed in epitheliform layer. It was common to observe peeling of these cellular elements, which, when extruded into the interior of the alveoli, showed all the intermediary aspects which distinguished them from large stimulated macrophages of vesicular nuclei.

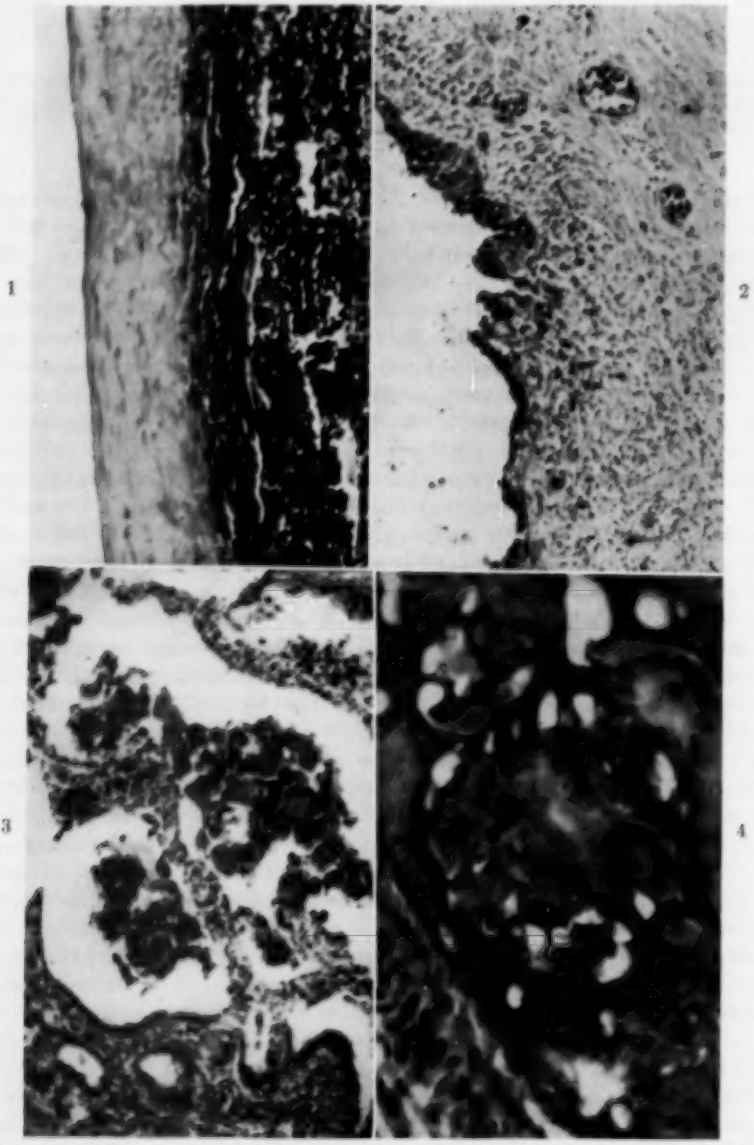


FIG. 1. Healed tuberculous cavity. A layer of collagenous bundles is in immediate contact with the cavity lumen. Pericavitary hyperemia. (12.5 × 10, Gömöri tric)

FIG. 2. Stretch of squamous epithelium lining a tuberculous cavity. (12.5 × 10, hematoxylin and eosin)

FIG. 3. Photomicrograph showing giant cells in the interior of alveolar spaces, bronchiolar hyperplasia and, at one point, calcification of the epithelium (*see* arrow). (12.5 × 10, hematoxylin and eosin)

FIG. 4. Giant cells, coated by mucus, within a bronchiole. (12.5 × 45, hematoxylin and eosin)

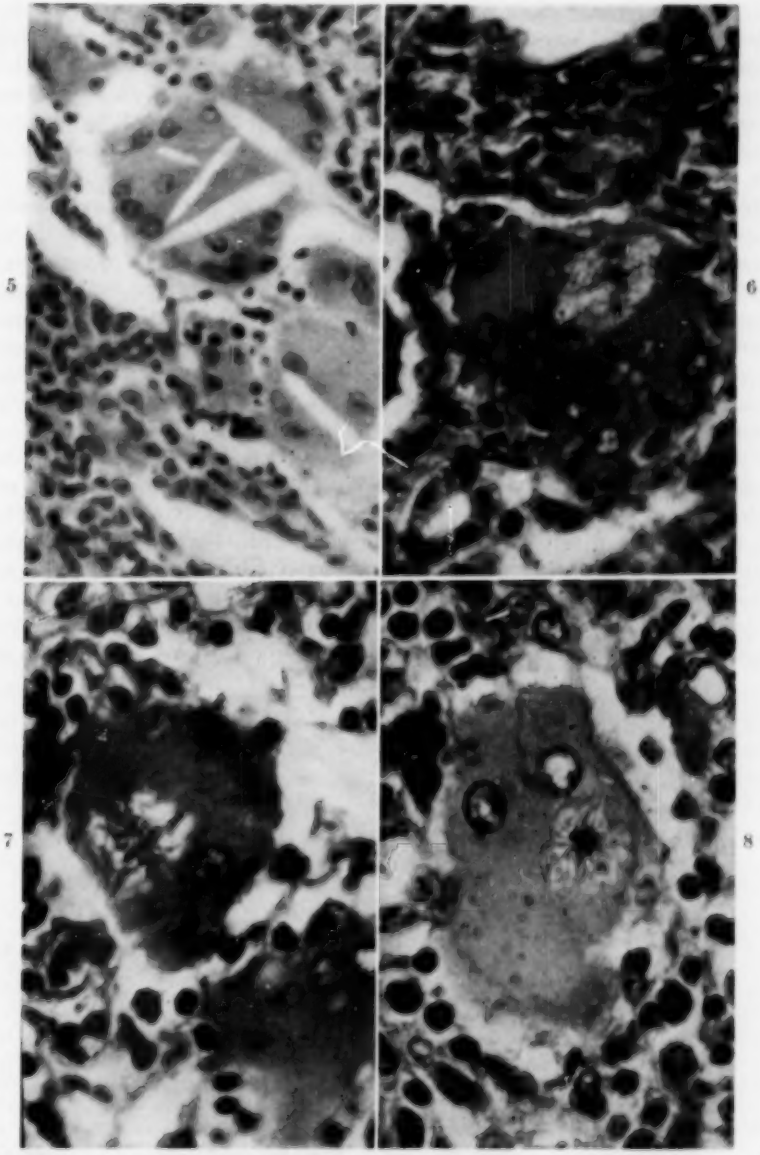


FIG. 5. Giant cells with crystal slits in the interior of air spaces. (12.5 × 45, hematoxylin and eosin)

FIG. 6. Giant cell with inclusions, suggesting the formation of asteroid bodies. (12.5 × 45, hematoxylin and eosin)

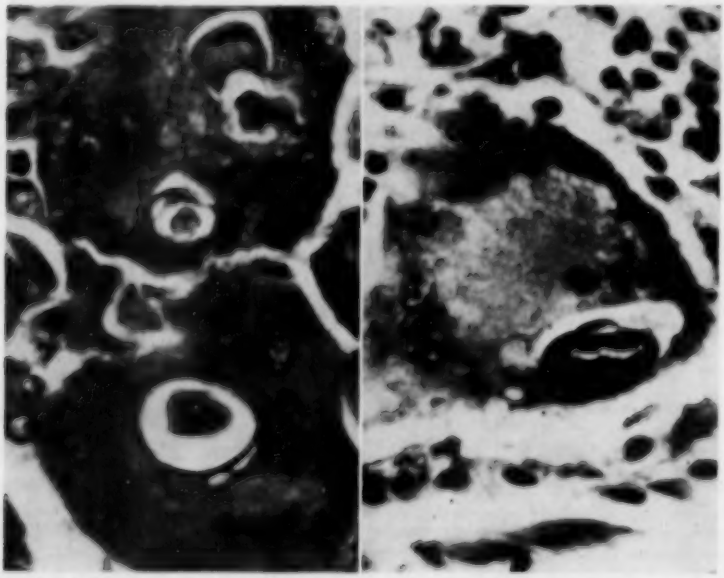
FIG. 7. Giant cell with an asteroid body in lung. (12.5 × 45, Gömöri tric)

FIG. 8. Giant cell with an asteroid body in a lymph node. (12.5 × 45, Gömöri tric)

Lymphocytic masses: Special mention should be made of the frequency with which lymphocytic masses were seen in interstitial location. Sometimes these masses, lined or not by an epithelioid layer, protruded into the air spaces. Along with typical adult lymphocytes, there were cells which were probably young forms of more abundant basophil cytoplasm and eccentric nucleus rich in chromatin. The center of these masses sometimes contained epithelioid and giant cells.

Bronchial lesions: No histopathologic peculiarity was observed in examination of the bronchial lesions. Of a total of 23 bronchi, 12 were found with epithelioid giant cell tubercles in the mucosa. In 4 patients there was simple hyperplasia of the epithelium, and in 9 there was metaplasia of this epithelium. In 10 patients the epithelium was partially or totally destroyed; in 8 the thickness of the basal membrane was striking. In the lesions from 4 adult patients, there were semi-destroyed cartilages replaced by bony tissue which, in places, included myeloid tissue. It is not known whether, in these 4 patients, the formation of the bony tissue had any relation to the effect of streptomycin or isoniazid.

Foam cells, giant cells with lipoid inclusions, asteroid and Schaumann bodies: In some cases it was noted that, within the alveoli, there were masses of cells with a spongy or xanthomatous appearance (foam cells). It was also observed, not infrequently, that there were large lipoid inclusions in the interior of giant cells. This fact, according to Denst (12), probably has no special significance as it is identical with that seen in other types of pulmonary infection. But the finding of Schaumann bodies, pointed out by Denst, is a very curious tissue reaction. Denst noted these in 2 of 11 surgical specimens from patients treated with iso-



FIGS. 9 and 10. Schaumann bodies within giant cells. (12.5 × 45, hematoxylin and eosin)

niazid (12). In a total of 56 specimens in the present study, asteroid or spiculated bodies, as well as inclusions which appeared to be precursors of such, were observed in only one case. Calcified Schaumann bodies were seen in 2 cases. Asteroid bodies have been found in a variety of pathologic conditions (14, 15). Schaumann bodies have also occurred in some chronic granulomatous diseases in animals, but, according to Rich, they have never been observed in lesions which were demonstrably tuberculous in man (16, p. 732).

Healing of cavitary walls: Sometimes following isoniazid therapy, the cavitary walls healed completely, producing roentgenographic images similar to those of air cysts. These cavitary walls were constituted, as was seen in 5 patients, of young fibrous tissue or collagenous bundles partially hyalinized. The fibrous tissue was in immediate contact with the cavitary lumen, with no cellular delimitation or with only small stretches of cells lined up in a continuous layer. These aspects are apparently the same as those described by Hein and Stefani (17, p. 185) as epithelization of the cavitary wall. In agreement with Purriel and associates (18), the present writers believe that these are not epithelial cells from the bronchiolar lining, but connective cells disposed in a continuous single layer. In only one patient was true squamous epithelium found in a previously drained cavity.

SUMMARY

The writers have analyzed the histopathologic aspects of the tuberculous lesions in 56 surgical specimens. All of the patients, with the exception of 3, received isoniazid for variable periods, usually several months. Although most of the patients had received streptomycin and para-aminosalicylic acid (PAS) in addition to isoniazid, some of the histopathologic aspects described were considered to be peculiar to the action of the latter drug. There are two principal reasons for this conclusion: (*a*) the histopathologic changes were never noted before with the isolated use of streptomycin and PAS; (*b*) they appeared in a clear and impressive manner in some patients in whom pulmonary resection was possible only after substantial improvement of the roentgenographic picture after months of treatment solely with isoniazid.

SUMARIO

Modificaciones de las Lesiones Tuberculosas en los Enfermos Tratados con Isoniacida

Analízanse aquí los apectos histológicos más interesantes de la lesión tuberculosa en 56 ejemplares quirúrgicos. Todos los enfermos, menos 3, tomaron isoniacida durante perfodos variables de tiempo, por lo general varios meses. Aunque la mayoría de los sujetos habían recibido estreptomicina y PAS, además de isoniacida, algunos de los aspectos histopatológicos descritos se consideraron como peculiares de la acción de la última por dos razones: no se habían notado jamás antes con el uso aislado de estreptomicina y PAS, y aparecieron en forma clara e imponente en algunos enfermos en que sólo resultó posible la resección pulmonar después de una mejoría substancial del cuadro radiográfico, a continuación de meses de tratamiento exclusivo con la isoniacida.

RESUME

Modification des lésions tuberculeuses chez les malades traités par l'isoniazide

Les aspects histologiques des lésions tuberculeuses provenant de 56 résections ont été analysés. Tous les malades, sauf trois, avaient reçu l'isoniazide pendant des temps variables,

habituellement plusieurs mois. Bien que, chez la plupart de ces patients, la streptomycine et le PAS aient été associés à l'isoniazide, certains des aspects histologiques décrits ont été considérés imputables à une action particulière de ce dernier composé, pour deux raisons: Ils n'avaient jamais été observé avec l'emploi unique de streptomycine et de PAS; ils apparaissaient de façon nette et impressionnante chez certains malades, quand la résection n'avait été possible qu'après amélioration substantielle de l'image radiographique à la suite d'un traitement de plusieurs mois avec l'isoniazide, exclusivement.

Acknowledgments

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A FIVE-YEAR FOLLOW-UP STUDY OF SIXTY-FOUR TUBERCULOUS PATIENTS TREATED WITH STREPTOMYCIN IN 1947–1948

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INTRODUCTION

The immediate or early therapeutic effects of streptomycin and several other more recently discovered antituberculous agents are well known and have been repeatedly documented. Of equal importance are the ultimate or late results of modern phthisiotherapy, for tuberculosis is so classically a chronic disease with relapses and remissions often extending over a period of many years. It is imperative, therefore, that, whenever available, follow-up reports be submitted giving the late results of antituberculous treatment.

The present report is a five-year follow-up study of the first tuberculous patients, 64 in number, who were treated with streptomycin[2] (1) in 1947–1948 while hospitalized at four of the New York State tuberculosis hospitals[3].

It is believed that the facts so obtained are, in certain obvious basic and fundamental respects, important in themselves and also when planning and when assaying the outcome of more modern antituberculous therapy. Steinbach and associates (2) and Canada and associates (3) have reported on similar studies at two and one-half and at three years, respectively.

PLAN OF INVESTIGATION

As, at the start of this study, the amount of streptomycin available was quite limited, hospitalized patients were very carefully chosen for treatment at conferences of staff members from the cooperating hospitals held specifically for this purpose. The three basic regimens and the several miscellaneous regimens were chosen in the same way (*see* table 4). The decisions as to daily dosage and length of treatment were based on information obtained from previous clinical trials (4, 5) and on the amount of streptomycin available at the time. Furthermore, as at the start of this clinical study and for many months thereafter streptomycin was the only antituberculous drug available, it was given alone and not in conjunction with other antituberculous drugs.

During the first weeks of the study, while streptomycin was being given, a review with the patients of their clinical symptoms and signs, together with physical, sputum (by microscopy and/or culture), and roentgenographic examinations were made each two weeks. Later on, these studies were repeated each month and still later on or after discharge from the hospital each two to six months as indicated. In addition, when there were symptoms or signs of laryngeal, bronchial, intestinal, or other tuberculous complications, or of nontuberculous complications, appropriate pretreatment examinations were made to

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[2] As a part of the Streptomycin-Tuberculosis Research Project of the American Trudeau Society.

[3] The Ray Brook State Tuberculosis Hospital, Ray Brook; the Hermann M. Biggs Memorial Hospital, Ithaca; the Homer Folks Tuberculosis Hospital, Oneonta; and the Mount Morris Tuberculosis Hospital, Mount Morris.

establish or exclude the presence of such. In those cases in which complicating conditions were demonstrated or strongly suspected, repeat laryngoscopic, bronchoscopic, barium meal, and/or other studies were carried out each month or more often during the period when streptomycin was being given and for some time thereafter. At each examination period the over-all course of each patient was reviewed and graded as "no change," "improved," or "worse" by noting the changes occurring in:

1. Clinical symptoms and signs such as temperature, pulse rate, sense of well-being, strength, appetite, dyspepsia, weight, cough, expectoration, hoarseness, wheezing, chest pain, hemoptysis, and dyspnea
2. The findings at physical examination
3. The extent and intensity of disease and cavity size as recorded on chest roentgenograms
4. Sputum character, quantity, and bacillary content
5. Blood counts and erythrocyte sedimentation rates
6. Laryngoscopic, bronchoscopic, barium meal, and other studies as indicated

Depending on the degree of change noted, the *improved* or *worse* categories were subdivided into *slight*, *moderate*, or *marked*.

The pretreatment data are recorded in tables 1, 2 and 3(*A*). The youngest patient was thirteen years of age, the oldest was sixty-three; 54 (84.4 per cent) were in the age groups thirteen to forty years; the sex distribution showed an approximate ratio of one male to two females; all but 3 patients were white (table 1).

TABLE 1

AGE, SEX, AND RACE DISTRIBUTION OF PATIENTS AT THE START OF TREATMENT WITH STREPTOMYCIN

Age			Sex		Race	
Years	Patients		Male	Female	White	Negro
13 to 20	14	84.4 per cent	3	11	14	
21 to 30	30		8	22	30	
31 to 40	10		4	6	7	3
41 to 50	4		4		4	
51 to 60	4		3	1	4	
More than 60	2		1	1	2	
Total	64		23	41	61	3

TABLE 2

EXTENT AND DYNAMIC STATUS OF THE PULMONARY TUBERCULOSIS; AND THE BACTERIOLOGIC STATUS AT THE START OF TREATMENT WITH STREPTOMYCIN

Extent			Dynamic Status		Bacteriologic Status	
			Active	Activity Undetermined	Positive for Tubercle Bacilli (by Concentration and/or Culture)	Negative for Tubercle Bacilli (by Culture)
Minimal	3	95.3 per cent	2	1	2	1
Moderately advanced	33		33		32	1
Far advanced	28		28		28	
Total	64		63	1	62	2

TABLE 3

ACTIVE TUBERCULOUS COMPLICATIONS

Site	*A* Number Present at the Start of the Original Period of Treatment with Streptomycin	*B* Number Appearing After the Original Period of Treatment with Streptomycin
Tracheal and/or bronchial	17	2
Laryngeal	7	2
Intestinal	3	
Orthopedic	1	5
Genitourinary	1	
Pleural	1	4
Lymph node	1	
Otic		1
Fatal hemoptysis		1
Total	31*	15†

* In each of 6 instances 2 complications were present in the same patient.
† In each of 2 instances, 2 complications were present in the same patient.

The extent of the pulmonary tuberculosis was *minimal* in 3 cases, *moderately advanced* in 33, and *far advanced* in 28; in all but one patient, the disease was classified as active (6). From the sputum of 62 patients, tubercle bacilli were isolated at the start of the original period of treatment with streptomycin. One patient who had had a thoracoplasty for moderately advanced pulmonary tuberculosis had previously had infective sputum; the remaining patient whose sputum was negative for tubercle bacilli by culture had minimal pulmonary disease and active sacroiliac disease, both diagnosed as tuberculous (table 2).

At the start of the streptomycin treatment period, thirty-one active tuberculous complications were present in 25 patients; 6 patients each had two such complications (table 3 (*A*)).

The dosage regimen and the length of the original streptomycin treatment

TABLE 4

DAILY REGIMEN, LENGTH OF PERIOD OF ORIGINAL TREATMENT WITH STREPTOMYCIN, AND LENGTH OF ORIGINAL COURSE OF STREPTOMYCIN TREATMENT VERSUS DEATHS DURING THE FIVE-YEAR PERIOD

Daily Regimen	Length of Period of Original Treatment	Number of Patients	Length of Original Course of Streptomycin Treatment versus Deaths During the Five-Year Period
1 gm. in one dose daily	56 days	17	6 deaths (35.3 per cent)
1 gm. in one dose daily	90 days	17	
1 gm. twice daily	90 days	17 (47)	6 deaths (12.8 per cent)
Miscellaneous regimens varied from 1 gm. each two days to 1 gm. twice a day	Varied from 90 to 180 days	13	
Total		64	12

TABLE 5

OVER-ALL COURSE DURING THE ORIGINAL STREPTOMYCIN TREATMENT PERIOD

No Change	Improved		Worsened		Total
	Slight	Moderate-to-Marked	Slight	Moderate	
8* (12.5 per cent)	28† (43.8 per cent)	25 (39.1 per cent)	1 (1.6 per cent)	2 (3.1 per cent)	64

* Of these 8 who showed no change, 6 died during the five-year follow-up period.

† Of these 28 who showed only slight improvement, 6 died during the five-year follow-up period. (Total, 12 deaths.)

period are given in table 4. Except for the group on miscellaneous regimens, one third of the patients received 1 gm. of streptomycin in one dose each day for fifty-six days; another third received the same daily dose for ninety days; the remaining third received 1 gm. of streptomycin twice daily each day for ninety days.

RESULTS

Course during original therapy: The over-all course of the patients in this study during the original streptomycin treatment period is shown in table 5: 8 patients showed no change, 28 improved slightly, 25 improved moderately to markedly, one became slightly worse, and 2 became moderately worse.

The 12 patients who died during the five-year follow-up period had pulmonary lesions which showed either no change or only slight improvement during the original streptomycin treatment period; this would appear to indicate that "no change" or only "slight improvement" during a few weeks of original streptomycin treatment in the type of disease treated in this study has unfavorable prognostic significance (table 5).

In the group of 17 patients treated for the shortest period of time, fifty-six days, 6 (35.3 per cent) deaths occurred during the five-year period of this study; in the remaining group of 47 patients who were treated for longer periods of time, 6 (12.8 per cent) deaths occurred during the five-year follow-up period. This favorable percentage with respect to deaths would appear to point toward a better prognosis for life for those patients treated for longer periods of time (table 4).

Subsequent chemotherapy: Following the original course of streptomycin treatment, 26 patients (40.6 per cent) received further antimycobacterial treatment of various types and regimens. Approximately the same percentage of patients in each of the original streptomycin regimens later received re-treatment with streptomycin or other antituberculous drugs. Considering these 26 patients at the end of the five-year follow-up period (table 6), the disease in 14 (53.8 per cent) was classified as inactive or arrested, in 6 (23.1 per cent) as active or activity undetermined; 6 (23.1 per cent) had died. Similar analysis (table 6) concerning those patients, 38 in number, who received no further antimyco-

TABLE 6

PATIENTS RE-TREATED WITH ANTIMYCOBACTERIAL AGENTS AND THEIR DYNAMIC STATUS AT THE END OF THE FIVE-YEAR FOLLOW-UP PERIOD

Patients	Dynamic Status at the End of Five-Year Follow-up		
	Inactive or Arrested	Active or Activity Undetermined	Dead
26 (40.6 per cent)	14 (53.8 per cent)	6 (23.1 per cent)	6 (23.1 per cent)

PATIENTS NOT RE-TREATED WITH ANTIMYCOBACTERIAL AGENTS AND THEIR DYNAMIC STATUS AT THE END OF THE FIVE-YEAR FOLLOW-UP PERIOD

38 (59.4 per cent)	24 (63.2 per cent)	8 (21.1 per cent)	6 (15.8 per cent)

TABLE 7

COLLAPSE AND/OR SURGICAL PROCEDURES CARRIED OUT IN 33 PATIENTS DURING THE FIVE-YEAR PERIOD OF THIS STUDY

Procedure*	Pneumothorax	Pneumo-peritoneum	Phrenic	Thoracoplasty	Resection	Total Procedures
Frequency	9	3	3	23	7	45 (in 33 patients)

* Multiple procedures (22 procedures) were performed in 10 patients.

bacterial therapy during the period of this study reveals figures (24 (63.2 per cent); 8 (21.1 per cent); 6 (15.8 per cent), respectively) which are slightly more favorable. This is as would be expected because those patients whose course had been unfavorable were often chosen for re-treatment.

Collapse or excisional therapy: During the five-year follow-up period, forty-five pulmonary collapse or surgical procedures were carried out in 33 (51.6 per cent) of the 64 patients in the study; in each of 10 cases, two or more such therapeutic methods were employed (table 7). Approximately 30 per cent of these collapse or excisional procedures were performed during the first six months after the start of the original streptomycin treatment period, 30 per cent also during the second six months, and another 30 per cent during the second year. The timing of the remaining few procedures was equally divided between the third, fourth, and fifth years. These results show that very early in the antimycobacterial therapy era it was recognized that such therapy was not definitive. In 31 patients, no collapse or surgical measures were performed; in several of this group the disease was not suitable for such treatment.

Development of tuberculous complications after completion of treatment: Following the original streptomycin treatment period, fifteen tuberculous complications appeared in 13 patients (table 3(*B*)). This clearly demonstrated that short courses of streptomycin (together with the other therapeutic measures employed) did not prevent the development of such unfavorable happenings. Four of these 13

TABLE 8

STATUS AT THE END OF THE FIVE-YEAR FOLLOW-UP PERIOD

Dynamic Status	Patients	
Inactive or arrested	38 (59.4 per cent)	81.3 per cent alive
Active or activity undetermined	14 (21.9 per cent)	
Dead	12* (18.7 per cent)	
Total	64	

* Deaths During the Five-Year Period:

Year	First	Second	Third	Fourth	Fifth	Total
Deaths	4	4	1	2	1	12

patients had had tuberculous complications at the start of the original period of streptomycin treatment. Nevertheless, the complications that developed after the original treatment period all involved sites different from those affected at the start of the five-year observation period.

It is interesting and important to note that 10 of the 12 patients who died during this five-year period had tuberculous complications that were either present at the start of the observation period or developed later. One of the patients who had no tuberculous complications died of unknown cause on the first postoperative day following a thoracoplasty; the other fatality occurred in a patient who had had no tuberculous complications and died solely from progressive pulmonary tuberculosis.

Ultimate outcome of the entire group: Except for those who died earlier, all of the patients were followed for a period of five years. Twelve (18.7 per cent) died during this follow-up period. One patient died following operation; one died of acute leukemia (together with advanced pulmonary and vertebral tuberculosis); one died of periarteritis nodosa (together with advanced pulmonary and vertebral tuberculosis). The other 9 deaths were caused by either progressive tuberculosis or tuberculous complications such as silicotuberculosis, bronchopleural fistula and empyema, and massive hemoptysis. Four patients died during the first year, 4 during the second year, one during the third year, 2 during the fourth year, and one during the fifth year (table 8).

Fifty-two patients (81.3 per cent) were alive at the end of the five-year follow-up period; in 38 (59.4 per cent), the disease was classified as inactive or arrested; and in 14 (21.9 per cent), as active or activity undetermined (table 8).

SUMMARY

A five-year follow-up study is reported of 64 adult tuberculous patients treated with 56- to 180-day courses of streptomycin in 1947–1948; it was possible to obtain the follow-up observations in 100 per cent of the group.

More than 95 per cent of the patients had active advanced pulmonary tuber-

culosis with tubercle bacilli in the sputum; in addition, approximately one-half had, or later developed, active tuberculous complications.

During the original streptomycin treatment period, the pulmonary lesion of 12.5 per cent of the patients showed no change; in less than 5 per cent, the lesion worsened; and in the remaining patients, approximately 80 per cent of the pulmonary lesions showed improvement. The outcome was more favorable in those patients who had been treated for the longer periods of time.

The 12 deaths occurred among those patients who showed either "no change" or only "slight improvement" during the original streptomycin treatment period. Ten of the 12 patients who died during the five years of this study had active tuberculous complications.

As viewed in the light of subsequent experience, the original courses of streptomycin therapy employed were obviously not adequate to be considered definitive treatment. In approximately 60 per cent of the cases, however, an inactive or arrested status was attained sooner or later and persisted throughout this five-year follow-up period. This statement must be interpreted with the knowledge that 40 per cent of the patients received re-treatment with antimycobacterial agents and that medical collapse or surgical treatment was used in approximately one-half of the cases.

The development of tuberculous complications was not prevented by the streptomycin and other treatment employed.

Approximately four-fifths of the patients in the study were alive at the end of the five-year follow-up period.

SUMARIO

Cinco Años de Estudio Subsecuente de Sesenta y Cuatro Tuberculosos Tratados con Estreptomicina en 1947–1948

Preséntase un estudio subsecuente de cinco años de 64 tuberculosos adultos tratados con series de 56 a 180 días de estreptomicina en 1947–1948; el estudio comprendió a 100 por ciento de los enfermos.

Más de 95 por ciento de esos enfermos tenían tuberculosis pulmonar avanzada activa con bacilos tuberculosos en el esputo; además, aproximadamente la mitad tenía, o manifestó después, complicaciones tuberculosas activas.

Durante el primitivo período de estreptomicinoterapia, 12.5 por ciento de los enfermos no manifestaron alteración; menos de 5 por ciento empeoraron; los restantes, aproximadamente 80 por ciento, mejoraron. El resultado fué más favorable en los tratados durante períodos más largos de tiempo.

Las 12 muertes fueron entre los enfermos que bien no habían revelado "la menor alteración" o sólo revelado "leve mejoría" durante el primitivo período de estreptomicinoterapia. Diez de los 12 enfermos fallecidos durante los cinco años de este estudio tenían complicaciones tuberculosas activas.

A la luz de las observaciones subsiguientes, las series de estreptomicinoterapia empleadas primitivamente no fueron manifiestamente suficientes para considerarlas como tratamiento definitivo; sin embargo, aproximadamente en 60 por ciento de los casos sobrevino tarde o temprano un estado inactivo o estacionado que persistió todo este período de cinco años de observación subsecuente. Hay que interpretar esta declaración con el conocimiento de que 40 por ciento de los enfermos recibieron re-tratamiento con agentes antimicobacterianos y de que se usó la colapsoterapia médica o quirúrgica aproximadamente en la mitad de los casos.

La aparición de complicaciones tuberculosas no fué impedida por la estreptomicina y el otro tratamiento empleado.

Aproximadamente cuatro quintas partes de los enfermos de este estudio se hallaban vivos al terminar el período de cinco años de observación subsecuente.

RESUME

Une période d'observation de cinq années chez soixante-quatre malades tuberculeux traités par la streptomycine en 1947–1948

Etude relative à une période d'observation de cinque année concernant soixante-quatre adultes tuberculeux ayant été soumis à des cures de streptomycine de 56 à 180 jours en 1947–1948; 100 pour 100 des malades ont pu être suivis.

Parmi ces malades, 95 pour 100 étaient atteints de tuberculose pulmonaire en activité avec crachats bacillifères; de plus, au moins la moitié d'entre eux avaient eu, ou présenté, des complications tuberculeuses évolutives.

Pendant la période initiale du traitement par la streptomycine, 12,5% des cas n'ont pas été modifiés, 5% se sont aggravés; les autres, environ 80%, se sont améliorés. Les conditions ultérieures les plus satisfaisantes ont été observées chez les patients ayant été traités pendant les périodes les plus longues.

Les 12 décès enregistrés se sont produits parmi les cas étiquettés "sans changement" ou "amélioration légère" au cours de la période de streptomycinothérapie initiale. Sur les 12 malades décédés au cours des cinq années de l'étude, 10 présentaient des complications tuberculeuses évolutives.

A la lumière de l'expérience ultérieure, les modalités des cures initiales de la streptomycinothérapie ne pouvaient donc être jugées adéquates et considérées comme un traitement définitif: toutefois, dans environ 60% des cas, il s'est produit plus ou moins tardivement une inactivité ou une stabilisation de la tuberculose qui s'est maintenue pendant la période d'observation de cinq années. Cette dernière assertion doit être interprétée en tenant compte du fait que 40% des malades avaient été soumis à une deuxième cure avec des agents antibactériens, et que le collapsus médical ou l'intervention chirurgicale avait été pratiqué dans approximativement la moitié des cas.

Le développement de complications tuberculeuses n'était pas prévenu par la streptomycine ou par les autres traitements utilisés.

A la fin de la période d'observation de cinq années, environ quatre cinquièmes des malades étudiés étaient encore vivants.

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A PSYCHOSOMATIC STUDY OF THE COURSE OF PULMONARY TUBERCULOSIS[1,2,3]

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INTRODUCTION

The relationship between psychological factors and pulmonary tuberculosis has been the subject of study for several decades. Earlier writers, for the most part tuberculosis specialists, concentrated on emotional and behavioral repercussions of the disease (1–4). As the concepts of psychosomatic medicine became more widely recognized, the emphasis shifted to a study of the role of psychological factors in the etiology of the disease (5–8).

The aim of the present study is an evaluation of some of the physical, psychological, and social factors affecting the course of pulmonary tuberculosis.

References in the literature to the role of psychological factors in the course of the disease are relatively few in number.

> Hayes (9), in 1930, wrote: "I think we should remember that, while we regard tuberculosis as one of the most curable of the chronic diseases, the prognosis in the average case of active tuberculosis is, at any given time, uncertain. It is uncertain because it depends on so many factors. The more important of these factors which determine the prognosis vary with the psychology of the individual patient." He believed that a favorable outcome depended to a large extent upon the ability of the physician to advise and intelligently guide the patient. Jelliffe (10) and Menninger (11) subscribe to the theory that tuberculous patients tend to internalize their aggression, producing self-destructive trends, and it is this mechanism which ultimately determines the outcome of the illness, and not the tubercle bacillus alone. Muhl, (12) in 1929, described "suicidal trends" in tuberculous patients, which she believes are "converted homicidal wishes, the patient having unconsciously identified herself with a member of the environment, and in wishing destruction for herself is surreptitiously attempting to obliterate this unconsciously unloved object." Hartz, (6) in 1944, concluded that "an individual may react to life situations with anxiety states, or other personal behavior in such a way as to interfere with healthy living, and these reactions may thereby become a most significant factor in the onset and course of clinical tuberculosis."
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> Ludwig (13), in 1947, wrote "The previous personality plays a definite part in the type of reaction elaborated. Some individuals actually welcome the disease as an escape from a difficult life situation. Conscientious persons may defy early symptoms, and neglect their care until the disease is far-advanced. The selfish and egocentric hasten to seek care, but are usually not bothered by concern for others."

[1] From the Allan Memorial Institute of Psychiatry, McGill University, Montreal, Canada.

[2] This research was made possible by a Dominion Provincial Mental Health Grant.

[3] Extracts from this article have been published in the second edition of *A Psychiatrist Looks at Tuberculosis* by E. D. WITTKOWER and appear here by arrangement with the publishers, National Association for the Prevention of Tuberculosis, London, England.

Wittkower (8), in 1949, stated that "sometimes it may be safer to assess the patient's prognosis on the basis of his personality and of his emotional conflicts than on the basis of the shadow on the film."

MATERIALS AND METHODS

A group of 80 patients with pulmonary tuberculosis were studied, 40 of whom had an unfavorable course and 40 of whom had a favorable course. The patients were seen at the Grace Dart Hospital in Montreal, the Royal Edward Laurentian Hospital in Ste. Agathe, the Mount Sinai Sanatorium in Prefontaine, and at their homes if they had been discharged from these hospitals. In order to reduce the number of variables, patients more than sixty years of age and those with a concurrent disease, such as emphysema or diabetes, which had interfered with the use of all available therapeutic procedures were excluded.

Unfavorable course: Criteria arbitrarily used for defining an unfavorable course were the presence of tubercle bacilli in the sputum and roentgenographic evidence of disease activity (*1*) after all available therapeutic procedures had been applied, or (*2*) after five years of the disease, whether or not all available treatment had been applied.

Favorable course: Criteria used for defining a favorable course were the absence of tubercle baciili from the sputum and roentgenographic evidence of apparently arrested disease. Patients in this group were matched with those with an unfavorable course for age, sex, and cultural background. Twenty patients were still in the hospital, ready for discharge, having been noninfectious for a minimum of six months. The other 20 patients had been discharged from the hospital for a period of at least one year, and had been followed by their own physician or a tuberculosis clinic during the post-discharge period.

The general background of the patients in the two groups is shown in table 1.

The investigation was carried out by a team of workers composed of a tuberculosis specialist, a psychiatrist, a psychologist, and a group of five social workers. The methods of examination were as follows:

The tuberculosis specialist reviewed the clinical histories of the patients and reported on each with regard to extent of disease at the time of first admission, nature and adequacy of treatment, and current status of the disease.

Each patient was psychiatrically examined for a period of one and one-half to three hours. A clinical history of the disease was obtained, including a history of the patient's reaction to the various stages of the disease—early symptoms, diagnosis, hospitalization, and treatment procedures. A detailed personal history was also taken in order to establish basic conflicts, character defenses, and the level of adjustment in occupational, interpersonal, sexual, and marital areas.

A battery of psychological tests was given, including a modified form of the Wechsler-Bellevue Intelligence Test, Rorschach, selected T.A.T. cards, Figure Drawing Test, Rosenzweig Picture Frustration Study, and Level of Aspiration Test.[4] Sixty-six patients were tested. Because of refusal, or severity of the illness, 6 of the

[4] Psychological testing was carried out by Miss Tanya Manuilow of the Department of Psychology of the Allan Memorial Institute of Psychiatry.

TABLE 1

GENERAL BACKGROUND OF THE MEMBERS OF THE TWO GROUPS

	Unfavorable Course	Favorable Course
Number	40	40
Sex:		
Male	27	27
Female	13	13
Age:		
Average	39.1 years	40.0 years
Less than 25	5.0 per cent	5.0 per cent
25–40	40.0 per cent	42.5 per cent
40–50	40.0 per cent	37.5 per cent
50–60	15.0 per cent	15.0 per cent
Country of Origin:		
Canadian born		
French	27.5 per cent	30.0 per cent
English	55.0 per cent	50.0 per cent
British born	2.5 per cent	5.0 per cent
European born	15.0 per cent	15.0 per cent
Marital Status		
Married	55.0 per cent	65.0 per cent
Single	45.0 per cent	35.0 per cent
Social Status		
Professional		5.0 per cent
Clerical	7.5 per cent	20.0 per cent
Skilled	40.0 per cent	20.0 per cent
Unskilled	37.5 per cent	27.5 per cent
Housewives	15.0 per cent	27.5 per cent
Average duration of illness from onset to time of examination	10.6 years	6.4 years
Average duration of time spent in the hospital	72.7 months	32.2 months

group with an unfavorable course and 8 of the group with a favorable course were not examined.

Forty patients, distributed equally between the two groups, were interviewed by the social workers. Whenever possible a member of the family was also seen.

OBSERVATIONS

Observations will be discussed under the headings of (*1*) family history, (*2*) prolonged exposure to massive infection, (*3*) extent of disease at the time of first admission, (*4*) treatment conditions, (*5*) pre-morbid personality, and (*6*) psychological findings. For convenience of presentation, the two groups will be referred to as the *Unfavorable Course Group* and the *Favorable Course Group*.

Family History

Fourteen of the 15 patients in the unfavorable course group who had a history of tuberculosis in parents or siblings, and 6 of the 12 patients in the favorable course group, gave a history of a death of tuberculosis in the family.

TABLE 2

STATUS ON FIRST ADMISSION

Classification	Unfavorable Course	Percentage	Favorable Course	Percentage
TB I	2	5.0	4	10.0
TB II	15	37.5	25	62.5
TB III	23	57.5	11	27.5
Total	40		40	

Prolonged Exposure to Massive Infection

Prolonged exposure to massive infection has been arbitrarily defined as exposure to an active case of pulmonary tuberculosis in the home for a period exceeding six months. When there was a question whether the patient under investigation or the other member of the family had the disease first, this case was excluded. Prolonged exposure to massive infection occurred in 13 of the unfavorable course group and 8 of the favorable course group.

Extent of Disease at the Time of First Admission

A comparison of the two groups on the basis of the roentgenographic findings at the time of first admission to the hospital indicated a significant relationship between the extent of the disease at the time of admission and the course of the disease (table 2). Patients with minimal or moderate lesions on admission by and large did well, while patients with advanced disease did badly.

Among the factors which determined the extent of the disease at the time of first admission were (*1*) delay between onset of symptoms and diagnosis, and (*2*) delay between diagnosis and admission to sanatorium.

Delay between onset of symptoms and diagnosis

The view commonly held that early diagnosis makes for a favorable course was confirmed. The diagnosis was made in the early stages of the disease in 17 (42.5 per cent) of the unfavorable course group and 29 (72.5 per cent) of the favorable course group. The disease was first detected on a routine roentgenographic survey in 5 of the unfavorable course group and 13 of the favorable course group. Early symptoms were recognized by the patient and medical advice was sought within a few weeks of their appearance in 12 of the unfavorable course group and 16 of the favorable course group.

Among the patients first admitted with far advanced disease, there was a lapse of six months or longer between the appearance of symptoms and diagnosis in 17 (42.5 per cent) of the unfavorable course group and 7 (17.5 per cent) of the favorable course group. Delay in diagnosis was due to failure of the physician consulted to recognize the illness in 5 patients (3 with an unfavorable course and 2 with a favorable course) and to conscious or unconscious denial of symptoms in 14 of the unfavorable course group and 5 of the favorable course group.

Tuberculosis is a much dreaded disease. It entails a threat to life at the worst,

and a transient abandonment of pleasure, loss of earning capacity, and prolonged hospitalization, at the best. Hence, it is hardly surprising that frequently patients deceive themselves consciously or unconsciously about the nature of their initial symptoms. This denial may be based on a self-deceiving, cheerful (manic) or defiant, pig-headed refusal to admit illness. Delay in patient-doctor contact may also be due to ignorance or stupidity.

Examples:

Conscious denial: O. S.—53-year-old foreman. "The first thing I noticed was tiredness. I was doing a lot of overtime and was blaming my tiredness on excess work. I guess you would say I was subject to colds. I was used to having a cough. I had a family of young children. I just couldn't see stopping work."

Unconscious denial: A. D.—33-year-old housewife. "I caught a cold. I didn't think anything of it. My husband wanted me to see the doctor but I said no, it isn't anything. Three or four days later I spit some blood. I still didn't listen to my husband. In our family when we have a little trouble we do not complain. One night I had some pain in my chest. My neighbor said to go to the clinic, wouldn't cost anything. When the doctor told me I had tuberculosis I was surprised. Tuberculosis! Gee! Me—tuberculosis!"

Delay between diagnosis and admission

Far advanced disease at the time of first admission was related to delay in hospitalization in 16 (40 per cent) of the unfavorable course group and in 5 (12.5 per cent) of the favorable course group.

The delay in hospitalization in 3 instances was due to unavailability of beds during wartime, and in the remainder to refusal to accept hospitalization. Some of the patients refused to go to the hospital because they felt duty-bound to carry on at their work rather than let their families down. Others rejected hospitalization because, consciously or unconsciously, they were unwilling to give up a close dependent relationship with parent or marital partner. Still others, averse to abandoning the pleasures of outside life, deceived themselves about the seriousness of their condition in a manic manner.

Example: Mrs. G. S., a 44-year-old mother of five children, refused to be admitted to the hospital for a period of two years after diagnosis. Her attitude was "I said right off I was not going. I had to take care of my children. I was very upset about the idea of coming to hospital. The only way they got me to come was to tell me I was dangerous to the children."

Treatment Conditions

Optimal treatment conditions were present in 15 (37.5 per cent) of the unfavorable course group and 30 (75 per cent) of the favorable course group.

Among the factors which determined whether or not optimal conditions were present were:

Availability of treatment

Six (15 per cent) of the unfavorable course group and 5 (12.5 per cent) of the favorable course group were treated before the introduction of chemotherapy and modern surgical procedures, or in tuberculosis hospitals where these were not available.

Cooperation of the patient

Refusal of surgery: Four (10 per cent) of the unfavorable course group and one (2.5 per cent) of the favorable course group refused major surgical procedures, such as thoracoplasty or lobectomy. Their refusal was based on a conscious or unconscious fear of mutilation or disfigurement. Sometimes the patient attempted to convince himself and the surgeon that the treatment wasn't really necessary in order to avoid acknowledging his deep fears. Well-marked narcissistic trends were present in all of the patients who refused surgery.

Failure to cooperate with general treatment regulations: Seven (17.5 per cent) of the unfavorable course group and 2 (5 per cent) of the favorable course group did not follow treatment regulations while in the hospital. Some adopted a rebellious attitude toward the hospital authorities and their regulations, delaying their return from legitimate passes, leaving the hospital without permission, drinking both in the hospital and while on leave, and participating in activities provided for patients of higher status.

Driven by a sense of guilt over their failure to fulfil obligations outside the hospital, several duty-bound persons overexerted themselves in their compulsive participation in hospital activities.

Interruption of treatment: In 17 (42.5 per cent) of the unfavorable course group and in 5 (12.5 per cent) of the favorable course group, treatment was interrupted by self-discharge. Irregular discharge may be due to many reasons, e.g., home worries or unsatisfactory patient management. As far as the personalities of the patients were concerned, it occurred most frequently in rebellious, duty-bound and family-bound persons.

Failure to follow medical advice in the post-discharge period: Ten (25 per cent) of the unfavorable course group and 5 (12.5 per cent) of the favorable course group gave a history of having had a relapse requiring rehospitalization which was directly related to failure to follow medical advice after leaving the hospital. Unwilling to lead a restricted life and to give up former pleasures, some patients resumed immediately their old activities, such as drinking, strenuous sports, dancing, et cetera; while others, motivated by an exaggerated sense of responsibility returned prematurely to jobs often involving long hours or strenuous physical exertion.

Examples:

Surgery: J. B., a 46-year-old foreman, refused a thoracoplasty. "Dr. C. said I should have an operation but I would rather stay in bed longer. I have seen some patients here. It would be better to die with a whole body than live with half a body. It might take longer, but to be all deformed! You would have to hide yourself." This patient, a strongly narcissistic man who related with obvious pride his sexual prowess and his ability to fight, had unconsciously related the mutilating operation to a threat to his manhood.

Rest cure. Rebellious attitude: R. B., a 27-year-old novelties salesman, had a history of psychopathic behavior beginning at adolescence, including excessive drinking, gambling, promiscuity, venereal infection, and several arrests for brawling. He stated: "Being in bed at nine o'clock was unusual for me. I wanted to be up all the time. I had a few drinks—if I had a bottle or two I slept better. I was on strict bed rest for a few months and wasn't supposed to go to the theatre but I went anyway. I really paid no attention to the cure. I arrived back late from passes. I just couldn't stay in bed. I was so restless. I guess I'm down as undisciplined."

Self-discharge. Over-dependent personality: O. M., a 27-year-old laborer, had left the hospital on two occasions. "Before you get sick you have lots of friends

—afterwards you have no more. I felt all alone—like starting a new life. I thought I was finished. I cried at night—didn't want to eat. I went to R. It was six hundred miles from home. Mother couldn't come to see me. The food wasn't good either. I left there to go back home."

Post-discharge period. Conscious denial: C. G., a 30-year-old insurance broker: "I was sent home to rest for another six months which I did not do as I was supposed to, and the lesion spread. I guess I was young, foolish and pigheaded." After another admission to the hospital and a two-stage thoracoplasty, the patient was again discharged. "It took me three months to forget I was in the hospital, even with surgery. The doctors couldn't tell me anything. I couldn't take good advice. I knew about tuberculosis but I didn't feel sick. My father had died of it. Even then I didn't know the seriousness of it."

Pre-Morbid Personality

Psychiatric studies of tuberculous patients have failed to establish a uniformity of personality type, but have demonstrated that, in tuberculosis, as in other diseases in which psychological factors are important in a multicausal etiology, the characteristic emotional conflict is between obtaining satisfaction of the need to be loved and cared for and the expression of aggression. Ruesch (14) in 1948, (in a paper entitled "Infantile Personality—the Core Problem of Psychosomatic Disease") stated: "Dependence requires control of hostility. Since infantile personalities cannot express tension verbally and in interpersonal relations, hostility has to be repressed, or expressed in terms of actions. In the former case tension states ensue, while in the second instance actions become destructive to self and the persons with whom the patient lives."

The presence of intense, for the most part unsatisfied, needs to be loved and cared for as well as the tendency to repress aggression or act it out in ways destructive to the self were found among all of the patients in this study. The manner of solving this conflict between dependence and aggression varied from a frankly parasitic, demanding attitude toward the world to a rigid rejection of dependence needs and an exaggerated striving for independence. The character defenses of the individual's personality, developed through childhood experiences, determined the type of compromise between the conflicting drives which was effected. It stands to reason that, the more successful the compromise, the more stable the personality, and that, the more stable the personality structure, the

TABLE 3

PRE-MORBID PERSONALITY

Course		Unfavorable Course	Favorable Course
Overtly insecure	28	14	14
Rebellious	8	6	2
Self-asserters	21	3	18
Self-drivers	13	10	3
Conflict-harassed	8	6	2
Unclassified	2	1	1
Total	80	40	40

better the means of dealing with external stresses and the less evidence of tension and anxiety.

* * *

What follows is an attempt to correlate the course of the disease with the premorbid personality of the patients studied in behavioristic and dynamic terms. While fully recognizing and admitting the shortcomings of any typology, for the purpose of presentation, a classification is used which was used by one of the writers (E. W.) in a previous publication. This classification is based on absence, presence, and nature of character defenses employed (table 3).

Overtly insecure

The overtly insecure patients carry childhood dependence over into adult life with little or no modification. Actively and unashamedly they seek gratification of their basic need to be loved and cared for. They show little ambition or drive. They are content with mediocre employment as long as they can be sure of a modicum of security. Marriage is frequently avoided because of its added responsibilities, as well as the patient's reluctance to give up an unbroken attachment to the parents or their substitutes.

Because they allow themselves to become so dependent on others, these persons are unusually susceptible to the trauma of loss or separation from the key figures in their environment. Reaction to loss or rebuff may be an outburst of hostility directed toward the depriving figure, but more often loss precipitates a state of overt anxiety or depression. Dynamically, the latter represents the turning back of the hostility onto the individual's own ego, and is experienced by the patient as a sense of unworthiness with overwhelming feelings of guilt. Alcoholism in these patients is partly a means of obtaining oblivion, and partly represents an expression of a need for the "bottle."

Individuals with this personality configuration were evenly distributed between the two groups under investigation. Differences in the course of the illness may be due to differences in the precipitating situation and in adaptability to hospital life.

In only one patient with a favorable course, in contrast with 8 with an unfavorable course, loss of, or permanent separation from, supporting figures preceded the onset of the illness. In the remainder, the patients' fate, it seems, was decidedly affected by their ability or inability to transfer their dependent needs to the hospital environment. Those who took kindly to hospital life made a speedy recovery, while those who resented it, sometimes to the point of self-discharge, did badly. "Suckers" do better than "biters."

Favorable course: E. B., aged fifty-eight, was the younger of two boys. His mother died soon after the patient was born, and his father remarried almost immediately. He was pampered and spoiled by his parents. Because his mother had died of tuberculosis, the patient was given a shot of gin and put to bed at the slightest sign of a cough or cold. He enjoyed the attention he received through his special status in the family, and greatly resented the arrival of his new half-brothers and sisters.

After being expelled from college for having gone on several drinking sprees, the patient tried his hand as a clerk. He failed. He progressively moved down on the oc-

cupational scale and had been employed in a low-class bar for several years when he developed tuberculosis. At twenty-five he married, and has had three children. Although his wife often chided him for his lack of ambition, they got along very well.

The patient's tuberculosis was picked up on a routine survey roentgenogram. He was admitted to the hospital within a few weeks, and was discharged as apparently arrested about a year later. In the hospital he was consistently cheerful, got along well with the staff and other patients, and enjoyed the rest and the care which he received. Although his illness was a strain on the family finances, he was unconcerned, knowing that he could, if necessary, borrow from his oldest married daughter. During the post-discharge period, the patient took long hours of rest, allowed his wife to look after him, and, anxious to avoid any overexertion, returned to work on a part-time basis only.

Unfavorable course: J. L., aged fifty-eight, grew up as the favorite son of well-to-do parents. In the midst of college education he impulsively married a girl three years older than himself, and quit college. Afterward he estranged himself from his parents, brother, and sisters largely by his irritable demanding nature, and also by his alcoholism. He made no attempt to find employment appropriate to his ability and education and chose a job as a sign painter, mainly because he could come and go as he liked. His three children left home in their teens and never came back. The final blow came when his wife, unable to tolerate the patient's drinking and irresponsible behavior, left without warning. The patient, now completely alone, became deeply depressed, was unable to work, and began to drink more and more heavily. He ate irregularly, and his health deteriorated rapidly. Finally, he sought medical advice and was found to have advanced pulmonary tuberculosis. He was admitted to the hospital and has been an inpatient for a period of five years. He left once against advice, began drinking again almost immediately, and returned with still further advanced disease. In the hospital he is irritable and demanding, primarily concerned with getting as many "extras" as he can manage, and totally uninterested in his recovery and discharge. "If I left I'd have no prospects at all. I'd have to look for a job—I have no money," he said.

Rebellious

Having grown up in an unsettled home atmosphere where domineering parents imposed their authority without an admixture of affection, persons in the "rebellious" group entered adult life with a chronic "grouse," easily kindled by frustration and restriction. Outwardly they may present a rough and gruff front, but behind it they long for love and affection just as much as their overtly insecure brethren. The rebellious attitude of these patients interfered with their treatment. They were unable to tolerate the regimentation and restrictions of the hospital, and reacted to them in the same manner as they had done as children. Resentment and hostility were expressed in breaking hospital regulations, drinking, leaving without permission, and, by and large, in making a nuisance of themselves. Without exception, patients with an unfavorable course in this group gave a history of one or more discharges against advice or on disciplinary grounds.

Only 2 patients of the 8 members of this group progressed favorably. Both of them were seen at the conclusion of their first admission to the hospital. It appears likely that the disease in these patients, just as in the others, would become progressive, on a prolonged follow-up, by their resumption of previous activities.

J. S., a 36-year-old molder, grew up as the only boy in a family of six children. His father was a surly, distant man who drank heavily and treated the patient's mother badly. The latter concentrated her attentions on the patient, and attempted to con-

trol his behavior by an oversolicitous nagging attitude. "She'd give me anything. You could always get what you wanted from her. She worried a lot about me."

At school the patient excelled in athletics and did badly academically. Because of his undisciplined behavior, he was threatened with expulsion on several occasions. At fourteen he quit and took a job as a laborer. He has had jobs at that level since.

When he was twenty-one, the patient married. Instead of establishing his own home, he went with his wife to live with his older sister. This did not work out, so they moved to his father-in-law's home. The patient worked irregularly, drank heavily, and embarked on extramarital affairs. When his wife finally demanded a separation, he returned to live with his mother.

For the next few years the patient drank steadily, was promiscuous sexually, and made only sporadic attempts to work. He quarreled with his mother, who badgered him about his dissolute habits. A year before entering hospital, the patient developed obvious symptoms of tuberculosis, which he disregarded. He was admitted to the hospital. A year afterwards he was discharged on disciplinary grounds for walking out repeatedly without permission. After two months at home he entered another hospital and left against advice a few months later. He was discharged from a third hospital for repeated alcoholic intoxication. While in the hospital, he quarreled frequently with the nurses and other patients.

He said "I was always bad tempered. Being sick made me nervous. I get fed up easily. That's when I walk out. At one place they threw me out for sneaking out Sunday mornings to get something to eat. They were looking for a chance to toss me out. I feel like I'm locked up. They just try to keep you here. I like to get out and see the boys. I never have trouble with the doctors, only the nurses. They are always picking on me." The last statement is meaningful in the light of the patient's attitude to his mother, upon whom he depended heavily, but whose oversolicitude he also hated and rebelled against. "I'm her only boy. We have arguments but she'd do anything for me. She never liked my drinking, or my being thrown out of hospitals. If Nurse S. is the cause of my being thrown out again, I'll slap her." Clearly, the patient displaced his unconscious hostility towards his mother to the situation in the hospital, and acted this out in his rebellious behavior.

Self-asserters

In these persons, dependency needs are concealed behind a facade of self-assertiveness. Aggression is channeled into constructive activity which is aimed primarily at achieving financial and social security. Thus, the character defense of self-assertiveness, making use as it does of sublimation, is a fairly effective one.

As one might expect, threats to financial and social security and the potential consequences for their family, rather than disruption of interpersonal relationships as in the previous groups, disturbed the emotional equilibrium of these persons.

The rate of recovery in this group is higher than in any other. Of 21 patients who comprised this group, 18 recovered. As these patients are also the emotionally best adjusted of all examined, one is apt to construct a connection between the two variables and to suggest that emotional adjustment makes for a favorable course of the disease, while emotional maladjustment previous to its onset and afterward influences it unfavorably. The 3 patients with an unfavorable course were acutely distressed by the hardships endured by their family as a result of the loss of their earning powers.

R. B., a 35-year-old manager of a bus terminal, grew up as the oldest of a family of eight. He was an active, healthy boy, did well in school, and excelled in athletics. His

father was an employee of a railroad, and had advanced to a responsible position relatively young. The patient thought of himself as being like his father, although he added "I wish I had his health. He doesn't care about anything—doesn't worry too much." His mother was a strict, rather distant woman, who expected her children to make something of themselves.

After completing a college commercial course, the patient spent a short time in the Canadian Army, and was then employed by a large transport company. He advanced fairly rapidly and was considered to be a conscientious, reliable employee. He married at twenty-five, and had three children.

His tuberculosis was picked up on a routine survey of company employees. He had noticed only increasing irritability and fatigue prior to the diagnosis. He received the news of his illness with incredulity. "I just couldn't believe it. Then I cried. When you have a wife and three kids, it's a shock." After arranging for his family's welfare during his hospitalization, the patient entered the hospital, where he was cooperative and cheerful, well-regarded by staff and fellow patients alike. During his illness his job was held for him and, between his savings and some help from social agencies, his family got along without hardship. He said "They even promised me a better job—told me I wouldn't have to work on shifts. I had every reason to get better."

Self-drivers

Dependency needs in patients representative of this group were completely covered up by character defenses. Their lives were governed by conscious and unconscious attempts to emulate, please, or placate their ambitious, driving, and, hence, ambivalently regarded parents whose image had become an integral part of their personality structure. They were tireless workers, conscientious and perfectionistic. Some of them went far beyond the boundaries of reality-determined behavior and carried their efforts to absurd extremes.

Characteristically, the onset of tuberculosis followed a period of overwork, and in most instances the patients disregarded their initial symptoms and failed to seek medical advice at an early stage.

Such persons take badly to hospitalization, which deprives them of a much needed motor outlet. True enough, they usually carry out rules and regulations to the letter, yet they feel guilty over being idle. Their pent-up tension may be discharged in general restlessness and/or undesirable activities at the hospital; while, on discharge, guilt over having "let their family down" combined with an ever-present compulsive drive prompted some of them to plunge prematurely into work and accept unsuitable occupations. Five patients with an unfavorable course left the hospital prematurely, apparently motivated by concern for the welfare of their family, but in fact or at least also by their inability to tolerate inactivity.

No wonder that persons who act in this manner have a poor chance of recovery. In 10 of the 13 patients with this personality configuration, the course was unfavorable. Two of them had a relapse while still at the hospital.

J. P., a 33-year-old Russian doctor, had come to Canada as a displaced person. Contrary to his hopes, he could neither obtain a license to practice medicine nor a job as an electrician, for which he had been trained as a refugee. Rather than hang about lazily and forced by the necessity to earn a living, he took a job as a day laborer digging postholes. After three or four months of strenuous labor, he began to lose weight, developed a cough, abundant sputum, an elevated temperature, and night sweats. Although a trained physician, he disregarded his symptoms and drove himself harder

than ever. "I couldn't afford to quit," he said, "I would have lost my job." Some eight months after the beginning of his symptoms he was unable to work any longer and went to a general hospital, where pulmonary tuberculosis was diagnosed.

Conflict-harassed

Patients in this group grew up in homes where a strongly repressive atmosphere prevailed. Their dependent relationship to their parents was complicated by a strong unconscious erotic attachment to one of the parents, usually of the opposite sex. As adults they were characteristically rigid, inhibited persons, harassed by feelings of guilt over sexual drives and hostile urges, the real source of which they were unable to place and to define. When faced by situations arousing anger or sexual excitation, appropriate action was inhibited, creating states of chronic emotional tension. Occasionally the childhood conflicts were acted out unconsciously in adult situations, as for example in the choice of marital partners. When repressive defenses were weakened or failed, frank psychoneurotic symptoms appeared.

This group is made up of 8 patients, in 6 of whom the course was unfavorable. Three of them were admitted to the hospital shortly after an early diagnosis, with moderately advanced disease, and received an optimal course of treatment. In spite of this they failed to respond to treatment, and the course of the disease was downhill. Other factors being optimal, it was believed that the unfavorable course of the disease was directly related to the presence of psychological conflicts. In these patients the conflicts produced states of chronically heightened emotional tension, manifested in symptoms of acute anxiety, spells of depression, and frank psychoneurotic symptoms such as phobias. In view of the clear evidence of intense guilt feelings, both conscious and unconscious, one cannot help but believe that the unfavorable course of illness is related to the unconscious needs for punishment which can be demonstrated in these patients. Succumbing to the disease thus symbolizes a need to suffer for fantasied misdeeds. The physiological link between the psychological and the physical processes cannot be demonstrated and can only be assumed. If one can conceive of emotional conflict lowering the resistance of the body to the invasion of the tubercle bacilli, then the linking process might be considered to lie somewhere in the area of this concept of resistance used by the medical specialists, but rather poorly defined.

L. F., a sales clerk, aged thirty-seven, had had a bad start in life. Her father, a butcher, a man of powerful physique, often maltreated his wife and his six children in his outbursts of temper. Despite her fear of her father, the patient was closely attached to him, and thought of herself as "the little woman of the house." In marked contrast to her father, the patient's mother was a mild-mannered, ineffectual woman, invalided by a chronic nerve disease. She passively accepted all the abuse heaped on her by her husband, and made no attempt to shield her children from his outbursts.

The patient grew up a shy, inhibited girl. During childhood she had many nervous habits including nail biting, bed wetting, and nightmares. She had what she referred to as "a terrific inferiority complex." She would lose her temper when teased, but added "I wasn't quick to lose it. It depresses me if I do, and I feel terribly guilty."

The patient completed only seven grades of school and had to give up her adolescent ambitions to be a ballerina or a sculptor because she had to stay at home to care for her invalid mother. She had very few boy friends because, as she says, "I wasn't allowed to

have dates. My father had to know all about the boy so I preferred to stay home rather than go through all that. I had it drilled into me that men were out to take advantage of me." She had never had any heterosexual experiences, but often found herself fantasying relations with boys she had met. "I had a few boy friends, but I could never indulge. I'd be afraid of losing my self-respect."

As she grew older the patient began to develop frank psychoneurotic symptoms, the phobic nature of which indicated her conflicts over repressed sexual urges. She stated "I used to get the feeling that something terrible was going to happen to me. I'd be afraid to go out alone—or to get on a streetcar. I've been afraid of the street for a very long time, and of going to movies, and of the dark." (In her fear of the street, the patient was expressing her unconscious wish to be a "street-walker," and displacing the anxiety which such an impulse would create for her to the street itself.)

When she was nineteen the patient developed symptoms of tuberculosis. She delayed seeing a doctor because of her shyness and went reluctantly to a hospital when the diagnosis was made. At first it was something of a lark—"The first time I was ever away from home," but this mood rapidly disappeared and was replaced by symptoms of anxiety. "I thought I was trapped. I felt as if the room was closing in on me, and I had no strength to do anything about it."

The patient has been in the hospital, with the exception of a two-year period at home, for the past eighteen years. Her attitude toward the illness suggests its unconscious significance for her. "I never took the attitude 'Why me?'—I just figured it was one of those things. I'm glad it's me rather than anyone in the family, because I wouldn't want to see any of them sick. It doesn't matter with me. I've always had a low opinion of myself. Maybe it's because I have no attachments. When I was home I couldn't rest when there were things to be done. If you see a handicapped woman trying to do something, even if it meant my getting sick, I couldn't let her do it. Not a day passes that I don't think of home and feel guilty that I can't help."

The patient has clearly described her unconscious masochistic pleasure in suffering, which the illness gratified. The need to suffer was derived from the intense guilt which she felt over her unconscious hatred of her mother and her strong erotic attachment to her father. These conflicts arose, as the history indicates, through the patient's identification of herself with her mother—"I thought of myself as the little woman of the house." This entailed an unconscious wish to be rid of her mother in order to have her father to herself. Guilt over these fantasies led to failure in adult sexual adjustment, and eventually, as the need for repression became greater, frank psychoneurotic symptoms.

The unfavorable course of the tuberculosis might be seen as being directly related to the presence of these conflicts, as an expression of the patient's unconscious need to suffer.

* * *

Psychopathology: An inordinate need for affection together with conflicts over aggression were found in all the patients studied. The configuration of the premorbid personality depended upon the character defenses developed during childhood. Dependency needs were either freely expressed, and their gratification openly sought; were concealed by a rebellious hostile front; were suppressed, while aggressive drives were sublimated in strivings for independence; or were repressed, with a reaction formation of compulsive self-driving behavior.

Patients in the overtly insecure group who reacted to frustration of their dependency needs with hostility ("biters") tended to do badly, while those who responded to frustration by seeking substitute supporting figures ("suckers") tended to do well. The "biters" directed the destructive urges aroused by frustration of their needs against the internal fantasied counterpart of the lost sup-

porting figure, to which they unconsciously turned when the real object of their dependent needs was lost. The "suckers," on the other hand, transferred their dependent needs to a substitute external object, the hospital and its staff, and found real gratification of their desires to be cared for. The association of the former psychological mechanism with an unfavorable course might be conceived of as an expression of the self-directed destructive forces.

Concealment of dependent strivings by a facade of rebellious hostile behavior was found to be associated with an unfavorable course. In contrast to the overtly insecure group, these patients, unable to form close relationships because of their hostile attitude, met continuous frustration of their need to be loved and cared for. Substitute gratification was sought in promiscuous behavior or alcoholism. Hostility was acted out directly in antisocial behavior—stealing, fighting, et cetera, often leading to entanglements with the law. The unconsciously self-destructive nature of these forms of activity is evident, and the association with an unfavorable course of tuberculosis becomes more meaningful in this light.

In the group of self-asserters, dependency needs were suppressed, and aggressive drives were sublimated in constructive activities, serving to maintain the patient's independence and, hence, feelings of security. There was an association between minimal financial stress on the patient's family during the hospitalization and a favorable course, which seemed to be related to the relative absence of guilt and anxiety in the patient. On the other hand, in the few members of this group who did badly, there was evidence of exaggerated concern over the welfare of the family who suffered considerable privation as a result of the loss of the patient's earning power during the illness.

Dependency needs in the self-drivers were strongly repressed, while aggressive and hostile urges were channeled into compulsive self-driving behavior. On the basis of an ambivalent identification with stern, ambitious parents who rewarded conscientious behavior, these patients drove themselves to live up to these standards. The hostility which formed a large part of the feelings towards the parents was channeled into self-driving behavior and contributed to its compulsive quality. The enforced dependency of hospitalization aroused feelings of guilt over failure to live up to the internalized standards of perfection of the parents. In attempting to avoid these guilt feelings, these patients overexerted themselves, both in hospital activities and in the post-discharge period, with a detrimental effect on the course of the illness.

In the conflict-harassed group, unresolved infantile conflicts over erotic and hostile-dependent relationships to the parents led to feelings of guilt, with unconscious masochistic pleasure in suffering and need for punishment, when the forbidden urges were aroused in adult life situations. An unfavorable course seemed to be related to these unconscious self-punitive trends.

Psychological Findings

Comparison of the two groups on the basis of the level of intellectual functioning showed no significant difference. Nor were there, in all tests given, significant differences between the two groups on rating of energy output.

Specific aspects of personality such as expression of aggression and dependency needs were investigated. The Rosenzweig Picture Frustration Study (constructed for the purpose of measuring extrapunitive, intrapunitive, and impunitive direction of aggression) failed to show any significant differences between the two groups (statistically evaluated by means of Fisher's t test). In the light of some characteristic remarks made by several patients, e.g., "I know what I would say in such a situation but you can't write it down," it appears that this test is an unreliable tool for measuring the expression of socially unacceptable impulses, and, hence, inadequate for our purpose.

The problem of the manner in which aggression was dealt with by the patients in the study was approached by rating unconscious hostility as expressed in three well-known projective tests, the Rorschach, Thematic Apperception Test, and Draw-a-Person Test. Comparison of the two groups showed that the pressure of unconscious hostility was higher in the unfavorable course group. Nineteen (47.5 per cent) of the unfavorable course group and only 9 (22.5 per cent) of the favorable course group gave evidence of moderate to strong degrees of repressed hostility. This is in agreement with the psychiatric evaluation of the two groups.

Ratings of unconscious guilt feelings and of self-destructive trends failed to differentiate the two groups.

Ratings of dependency needs, as measured by the Rorschach, Thematic Apperception Test, and Draw-a-Person Test, showed that both groups had equally strong dependency needs, again paralleling the psychiatric evaluation of the pre-morbid personality. Important differences were observed regarding the manner in which these dependency needs were handled. Twenty (50 per cent) of the unfavorable course group revealed marked ambivalent attitudes as compared with 11 (27.5 per cent) of the favorable course group. Emotional ambivalence may be regarded as indicating a tendency to react to frustration of dependency needs with hostility ("biters"). The relationship of this to the course of the disease has been discussed.

The unfavorable course group showed a greater pressure of dependency needs as expressed in terms of need for affection and social acceptance, and for submission to authority. This would be expected to lead to exaggerated demands for attention from hospital authorities, as well as lack of feeling of personal responsibility in reaching recovery.

The favorable course group appears more mature, less ambivalent, and less conflicted over dependency needs, less concerned about getting attention, and more capable of accepting responsibilities. A readiness of the favorable course group to verbalize the "alcohol" theme more frequently than the unfavorable course group suggests that they were more inclined to act out their cravings for the "bottle" and thus more likely to accept dependency needs without conflict. This is consistent with their ability to transfer dependency needs to the hospital.

A male authority figure on one of the Thematic Apperception Test pictures was more frequently identified as a doctor than as a father by the favorable course group than by the unfavorable course group. This observation would suggest that

the favorable course group were able to deal with the stress of adjustment to hospitalization at a more mature level than the unfavorable course group, who tended to react at a more infantile level with reactivation of childhood conflicts in their relations with their parents. In a sense, dealing with reactivated childhood problems was more important than dealing with the disease itself.

Finally, certain aspects of the Rorschach results were analyzed in order to obtain a measure of the patient's flexibility. It was found that rigid persons prevailed in the unfavorable course group and flexible persons, i.e., persons capable of adaptation to adverse circumstances, in the favorable course group. Such a basic psychic quality as flexibility is considered of primary importance for successful psychotherapy. It is not surprising to find that it seems to be also essential for a successful adjustment to any stress. Flexibility permits the patient to find substitute gratifications for those which had to be abandoned as a result of the illness and its treatment and, thus, reduces the total amount of his frustration, aggression, and resentment, factors that tend to affect the course of treatment in an unfavorable way.

SUMMARY

Two matched groups of 40 patients with pulmonary tuberculosis, one with an unfavorable course of the disease and one with a favorable course, were studied by a team of workers composed of a tuberculosis specialist, a psychiatrist, a psychologist, and five social workers.

Reasons for delay in diagnosis and for delay between diagnosis and admission to the hospital were discussed. A favorable course was associated with optimal treatment conditions. Whether or not optimal treatment conditions were present depended to a large extent on the cooperation of the patient. The configuration of the pre-morbid personality was related to the course of the disease.

The following *practical conclusions* were drawn from the observations made:

A knowledge of the patient's background and personality is of help in deciding upon the best manner of communicating to him the diagnosis and planning the course of action. Forewarned is forearmed when a severe emotional reaction may be anticipated. A sympathetic awareness of the problems of the individual is necessary to deal with the situation adequately.

Many patients object strenuously to entering a hospital, and the reasons given for the objection may appear valid, but may not necessarily be the real reasons. Getting the patient to the hospital requires understanding on the part of the doctor in order to overcome the patient's fears and misapprehensions regarding the nature of his disease and its treatment. For example, the aid of a social worker is often essential, particularly in those cases in which the threat of stress to the patient's family may influence him to reject hospitalization.

A knowledge of the patient as an individual, with all of his fears, worries, and resentments, is essential for optimal treatment. Conscientious, duty-bound patients should be encouraged to do less than they feel is expected of them, and anxious, overdependent patients should be encouraged to do more than their

fear of reverses lets them. Refractory, hostile patients need an opportunity to air their grouses without fear of retaliation from the hospital authorities.

Fear of radical surgical procedures presents a serious therapeutic problem, and may require psychiatric advice.

There are many reasons for self-discharge from the hospital. Patients may discharge themselves because of poor hospital management, unsatisfactory patient-doctor relationships, home worries, or factors arising from their personalities. Self-driving patients cannot tolerate the feelings of guilt aroused by inactivity, while some overtly insecure persons long for the love and affection upon which they depended so heavily while at home. Rebellious patients unconsciously act out their resentment and anger by leaving the hospital or engaging in harmful activities.

The post-discharge period presents problems which will vary with the temperament of the individual patient. Some will hurry back to their jobs and overexert themselves, while others, fearful of relapse, will remain bound to the routine which they learned in the hospital. Still others will return to their former pleasures and rapidly forget the unpleasant and inconvenient features of their disease. Personality factors such as those mentioned may lead to behavior which results in relapse. Due regard for these factors is essential in the after-care. Recognition of them may prevent relapse.

SUMARIO

Estudio Psicosomático de la Evolución de la Tuberculosis Pulmonar

Dos grupos comparables de 40 tuberculosos pulmonares, uno con evolución desfavorabe y el otro favorable de la dolencia, fueron estudiados por un grupo de técnicos compuesto de un tisiólogo, un psiquíatra, un psicólogo y cinco asistentes sociales.

Discutiéronse las razones de la tardanza en el diagnóstico y de la tardanza entre el diagnóstico y el ingreso en el sanatorio. La evolución favorable se vinculó con condiciones óptimas de tratamiento, dependiendo en gran parte la existencia o falta de éstas de la cooperación del enfermo. La configuración de la personalidad premorbosa se relacionó con la evolución de la enfermedad.

De las observaciones efectuadas se sacaron las siguientes conclusiones prácticas: el conocimiento de los antecedentes y la personalidad del sujeto resulta de ayuda al determinar la mejor manera de comunicarle el diagnóstico y de proyectar el plan de acción. Prevenido significa preparado cuando cabe esperar una intensa reacción afectiva. Para atender adecuadamente a la situación se necesita una comprensión benévola de los problemas del individuo.

Muchos enfermos se oponen enérgicamente al ingreso en un sanatorio y las razones que ofrecen para su oposición tal vez parezcan legítimas, pero quizás no sean las verdaderas razones. La entrada del enfermo en el sanatorio requiere comprension de parte del médico para vencer los temores y conceptos erróneos que abriga el sujeto acerca de su enfermedad y del tratamiento de la misma. Por ejemplo, la ayuda de una asistente social resulta a menudo indispensable, sobre todo en los casos en que el peligro de que sufra la familia puede impulsar al enfermo a rechazar la hospitalización.

Para el tratamiento óptimo es indispensable un conocimiento del enfermo, con todos sus temores, preocupaciones y resentimientos. A los escrupulosos y esclavos del deber hay que persuadirlos a que hagan menos de lo que crean que se espera de ellos, y a los ansiosos y sumisos hay que alentarlos a que hagan más de lo que les permite hacer su temor a fracaso. Los enfermos refractarios y hostiles necesitan ocasion de ventilar sus querellas sin temor a represalias de parte de las autoridades del hospital.

El temor a procedimientos quirúrgicos radicales plantea un grave problema terapéutico y acaso requiera consejo psiquiátrico.

Hay muchos motivos que impulsan a los enfermos a abandonar el sanatorio. Los enfermos pueden irse debido a deficiencias en la dirección del sanatorio, poco satisfactorias relaciones entre médico y paciente, preocupaciones domésticas o factores creados por sus personalidades. Los abnegados no pueden tolerar la sensación de culpa que engendra en ellos la inactividad, en tanto que algunas personas por demás inseguras ansían el amor y la afección a que estaban tan atenidos en sus hogares. Los indóciles despliegan inconscientemente su resentimiento y furia abandonando el sanatorio y dedicándose a tareas nocivas.

El período de la post-alta plantea proeblemas que variarán conforme al temperamento del enfermo dado. Algunos volverán a toda prisa a sus quehaceres y trabajarán a exceso, mientras que otros, temiendo recaídas, se estacionarán en la rutina que aprendieron en el sanatorio. Otros más retornarán a sus placeres anteriores, olvidando rápidamente los puntos desagradables e inconvenientes de su dolencia. Factores de la personalidad por el estilo de los mencionados tal vez motiven un comportamiento que culmina en una recidiva. La debida consideración de esos factores es indispensable en el posttratamiento, pues su reconocimiento puede impedir las recaídas.

RESUME

Une étude psychosomatique au cours de la tuberculose pulmonaire

Deux groupes comparables de 40 malades atteints de tuberculose pulmonaire, l'un comprenant les cas à évolution défavorable, l'autre les cas défavorables, ont été étudiés par une équipe d'investigateurs composée d'un spécialiste de la tuberculose, d'un psychiatre et de cinq assistantes sociales.

Les causes du délai entre le diagnostic et l'admission au sanatorium sont étudiées. Une évolution favorable était associée aux conditions de traitement les meilleures. L'existence de conditions de traitement les plus satisfaisantes dépendait dans une large mesure de la coopération du patient. La configuration de la personalité avant la maladie était en relation avec l'évolution de la maladie.

Les conclusions suivantes ont été déduites des observations: la connaissance des antécédents et de la personalité du patient est utile pour décider de la meilleure manière d'informer le malade du diagnostic et établir un programme de traitement. Etre averti est être mieux préparé à envisager la forte réaction émotionnelle. Une compréhension sympathique des problèmes qui se posent pour l'individu est nécessaire pour traiter la situation de manière adéquate.

De nombreux malades s'opposent vigoureusement à l'entrée au sanatorium et les raisons de leur refus peuvent sembler valables; elles ne sont pas nécessairement les vraies. Pour amener le patient à accepter l'entrée en sanatorium, le médecin doit faire preuve de compréhension pour obvier aux craintes et aux idées fausses du malade à l'égard de la nature de sa maladie et de son traitement. Par exemple, l'aide d'une assistante sociale est sonvent essentielle, surtout dans les cas où le malade peut refuser l'hospitalisation en raison des difficultés que celle-ci entraîneraient pour sa famille.

La connaissance du malade, en tant qu'individu, de ses craintes, de ses soucis et revendications est indispensable à la réalisation du traitement le plus favorable. Il y a lieu d'encourager les malades consciencieux, soucieux de leurs obligations, à faire moins qu'ils n'estiment nécessaire, et les malades anxieux et timorés à faire plus que ne leur permet leur crainte d'accidents. Les malades réfractaires et hostiles doivent avoir la possibilité de faire connaître leurs griefs sans crainte de représailles de la part de l'administration de l'hôpital.

La peur des interventions chirurgicales représente un problème thérapeutique sérieux et réclame l'avis du psychiatre.

Il y a de nombreuses raisons pour que le malade quitte l'hôpital de son propre chef. Les malades peuvent le quitter à cause d'une mauvaise administration hospitalière, de mauvais rapports entre le médecin et le malade, de soucis familiaux ou de facteurs dérivant de la

personalité du patient. Les malades pleins d'énergie ne supportent pas le sentiment de culpabilité déterminé par l'inactivité alors que les sujets anxieux, timorés ont besoin de l'amour et de l'affection sur lesquels ils s'appuyaient lorsqu'ils étaient en famille. Les malades hostiles démontrent inconsciemment leurs ressentiments et leur colère en quittant l'hôpital ou en se livrant à des activités dangereuses.

La période post-sanatoriale présente des problèmes qui varient avec le tempérament individuel du malade. Certains se hâtent de reprendre leurs occupations et se fatiguent, tandis que d'autres, de crainte d' une rechute, restent fidèles à la routine sanatoriale sur laquelle ils s'appuyaient. D'autres encore se livrent de nouveau à leurs distractions antérieures et oublient rapidement les ennuis et inconvénients de leur maladie. Les facteurs de la personalité, tels que ceux mentionnés, peuvent conduire à un comportement qui cause la rechute. Une attention suffisante à l'égard de ces facteurs est essentielle dans la post cure. Lorsqu'ils sont reconnus les rechutes peuvent être prévenues.

Acknowledgments

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CLINICAL USE OF POTASSIUM PARA-AMINOSALICYLATE (KPAS)[1, 2]

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INTRODUCTION

Para-aminosalicylic acid (PAS), in conjunction with streptomycin or isoniazid, is of proved value in the treatment of tuberculosis. Many patients are unable to derive the full benefit of PAS, however, because of commonly associated side effects, chiefly anorexia, nausea, vomiting, and diarrhea. The sodium salt and other preparations of PAS have been utilized in efforts to overcome these untoward reactions, generally with only limited success. For example, a recent survey at the Eagleville Sanatorium revealed that, of 62 patients who had received PAS in the past, 44 (71 per cent) had significant symptoms of intolerance. Of an additional group of 38 patients who were receiving PAS at the time of the survey, 8 (21 per cent) had undesirable side effects. Thus, reactions to PAS occurred in over half of these 100 patients. This experience, as well as that of others, emphasizes the need for improved PAS medication.

A parallel situation existed for some time with para-aminobenzoic acid (PABA), a drug closely related to PAS, chemically and in dosage requirements. Extensive investigation of the clinical use of PABA compounds, however, revealed that the potassium salt, administered in the form of a 10 per cent solution, was far better tolerated than the acid (PABA) or its sodium salt (NaPAB) (1, 2). It was postulated that the same relationship might hold true for the potassium salt of PAS.

Accordingly, the present study was undertaken to determine the usefulness and "patient-acceptance" of this new preparation, namely, potassium para-aminosalicylate (KPAS).[3] The present report summarizes experience with the clinical use of KPAS from November 14, 1953 to August 1, 1954.

MATERIAL AND METHODS

Patients: A total of 64 patients with tuberculosis have received KPAS therapy to date. Included were 60 subjects with pulmonary tuberculosis, one with tuberculous cervical adenitis, 2 with tuberculosis of the hip, and one with Pott's disease. Thirty-five of the patients were hospitalized at the Eagleville Sanatorium, Eagleville, Pennsylvania; 18 at the Episcopal Hospital, Philadelphia; 5 at the Temple University Hospital; and 6 were treated on an outpatient basis. There were 47 males, whose ages ranged from 21 to 74 years (average 48.2 years); and 17 females with ages ranging from 21 to 48 years (average 31.5 years). Fifty-one of the patients were whites, while 13 were Negroes. From the outset, patients with histories of intolerance to PAS were deliberately solicited, as the principal

[1] From the Department of Internal Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania; and the Eagleville Sanatorium, Eagleville, Pennsylvania.

[2] This study was aided by a research grant from the Temple University School of Medicine.

[3] The Glenwood Laboratories, Inc. of Teaneck, New Jersey, manufactured and contributed most of the potassium para-aminosalicylate (Paskalium®) used in this study.

objective of the study was to determine patient tolerance to KPAS. Only patients with far advanced renal disease were purposely excluded from the study.

Method of administration: The KPAS administered to the patients was supplied by the manufacturer[3] as an anhydrous salt of high purity which contained 80 per cent PAS and 20 per cent potassium; that is, 1 gm. of KPAS supplied 0.8 gm. of free PAS. The preparation is very readily soluble and was administered to the patients in the form of a 10 per cent solution, using potable tap water as the solvent. The solution has a pale amber color and darkens on exposure to ultraviolet light. For this reason, the quantity prepared for any individual patient at one time was limited to one liter and the solution was kept refrigerated.

Dosage regimens: In general, patients were started on doses of 20 ml. or 2 gm. of KPAS (1.6 gm. of PAS), four times daily. This was raised at the end of one week by increasing the four doses to 25 ml., each, or by adding a fifth dose of 20 ml. At the end of the second week, the amount was again increased, and the patient received four doses of 30 ml., or 3 gm. of KPAS (2.4 gm. of PAS), or six doses of 20 ml. amount. Patients remained on doses of 30 ml., four times daily, or 20 ml., six times daily for maintenance therapy.

The usual total daily dose, therefore, was 120 ml. or 12 gm. of KPAS (9.6 gm. of PAS). This amount was employed because it corresponded to that prescribed for PAS or NaPAS in the institutions where this study was carried out. Its continued use was supported by the plasma PAS concentration studies to be detailed below. In some patients with mild renal impairment, however, the daily amount was limited to 100 ml. Patients severely ill with tuberculosis were given 150 ml. or 15 gm. KPAS (12 gm. of PAS) daily.

Individual doses were given after meals and at bedtime to patients on four doses daily; additional interval doses were given mid-morning and mid-afternoon to subjects on a six-dose schedule. Small interval and bedtime feedings were often given at the same time as the KPAS. Citrus juices were found to be relatively effective in masking the bitter-salty taste of the drug for the occasional patient who objected to this taste. Some patients developed symptoms of gastrointestinal discomfort if stale or unrefrigerated solutions of KPAS were given. This was avoided by refrigeration of the solution.

RESULTS

Patient Tolerance of KPAS

The results of KPAS treatment in so far as patient tolerance and acceptability are concerned are given in table 1. The patients are divided into two groups according to whether or not they had had prior PAS or NaPAS therapy.

Group A includes 43 patients who had had such therapy and, of these, 38 (88 per cent) were intolerant to either PAS or NaPAS to such a degree that treatment was either stopped or continued in doses of less than 8 gm. daily. Of this same group of patients, 40 (93 per cent) had no difficulty whatsoever when taking 12 gm. of KPAS daily.

Three patients (7 per cent) of *Group A* are listed as intolerant to KPAS. One was a woman who stated that therapy produced increased bulkiness of the stool, thereby leading to irritation and slight bleeding from pre-existing hemorrhoids.

TABLE 1

SUMMARY OF TOLERANCE RESULTS IN 64 PATIENTS TREATED WITH POTASSIUM PARA-AMINOSALICYLATE (KPAS)

Duration of KPAS Therapy	Total Number of Patients	Group A			Group B		Total Groups A and B	Number on KPAS at Present	Discontinuance of KPAS Therapy	
		Number Previous PAS or NaPAS	Number Intolerant of PAS or NaPAS	Number Intolerant of KPAS	Number No Previous PAS	Number Intolerant of KPAS	Number Intolerant of KPAS		Number of Patients	Reasons for Discontinuance
months										
>6	11	5	5	0	6	0	0	11	0	
4-6	11	8	7	1	3	0	1	10	1	1 death due to tuberculosis
2-4	13	6	7	6	7	0	0	12	3	1 death due to tuberculosis, 1 uncooperative patient, 1 patient transferred
<2	27	22	19	2	5	0	2	13	14	5 patients transferred, 2 clinical trial only, 2 intolerance to KPAS, 3 intercurrent illness, 2 uncooperative
Totals	64	43	38	3*	21	0	3*	46	18	
Per cent			88	7		0	4.7			

* Untoward symptoms: 1 irritation of hemorrhoids: drug discontinued; 1 anorexia and mild diarrhea: drug discontinued; 1 subjective complaints of paresthesias, vertigo, flank pain: drug continued in suboptimal dosage.

Another woman developed symptoms of anorexia and mild diarrhea during each of two ten-day courses of KPAS medication. The third patient listed in this category was a man who has continued to take KPAS in doses of 60 to 80 ml. daily. His reactions to KPAS and other drugs have been difficult to evaluate, partly because of personality traits and partly because of the presence of active bilateral pyelonephritis. As he has not been able to take 12 gm. of KPAS daily, he has been arbitrarily classified as being intolerant. It is to be noted, however, that all 3 of these subjects had exhibited severe gastrointestinal symptoms, including vomiting and diarrhea, from PAS prescribed in the past.

Group B in table 1 is comprised of 21 patients who had not received previous PAS therapy. All 21 (100 per cent) of this group have tolerated KPAS therapy without difficulty. Thus, 61 of 64 patients in both groups have accepted KPAS therapy.

The drug has been discontinued in 18 cases for the following reasons: Six patients were transferred to institutions where continued administration of the compound was not feasible; 3 patients developed intercurrent illnesses; 3 patients failed to cooperate; 2 were stopped, as indicated above, because of intolerance to KPAS; 2 patients died as a result of their disease; and, in 2 instances, the KPAS was given only on a clinical trial basis.

As of August 1, 1954, 11 patients had been on continuous KPAS therapy for more than six months, and an additional 26 subjects had been treated from two

to six months. No adverse effect has been observed in patients with such non-tuberculous complications as mild renal insufficiency (9 cases), congestive heart failure (3 cases), severe diabetes mellitus (1 case), scleroderma (1 case), sickle-cell anemia (1 case), ulcerative colitis (1 case), peptic ulcer (1 case), and systemic lupus erythematosus (1 case).

Toxicity Studies

Laboratory studies were performed on 14 patients who were on continuous KPAS therapy for periods of six to thirty-five weeks. Complete blood counts and urinalyses were done at weekly to monthly intervals, with an average of five blood examinations and six urinalyses per patient. No evidence of toxicity was found in these studies. Repeated blood urea nitrogen determinations revealed no increase in values in tests on 8 of the patients known to have pre-existing renal disease.

Serum potassium concentrations were done in 13 cases and showed no significant change when performed in the fasting state and repeated one to two hours after a 30 ml. dose of KPAS. Conventional liver function studies were performed on 3 patients before and during treatment and revealed no changes incident to KPAS therapy.

Plasma concentrations of KPAS: The PAS concentration (3) was determined on plasma specimens obtained from 26 patients taking KPAS, and from 15

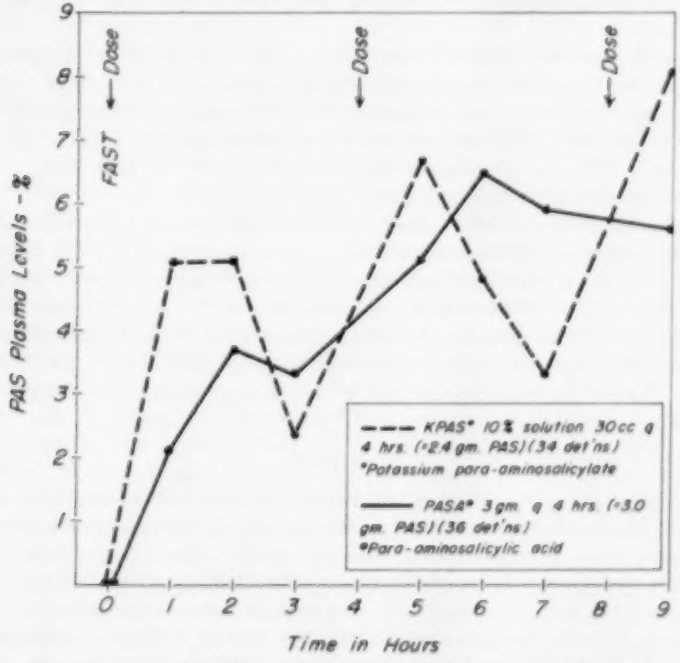

FIG. 1. Average plasma PAS concentrations after 3 gm. doses of indicated compound.

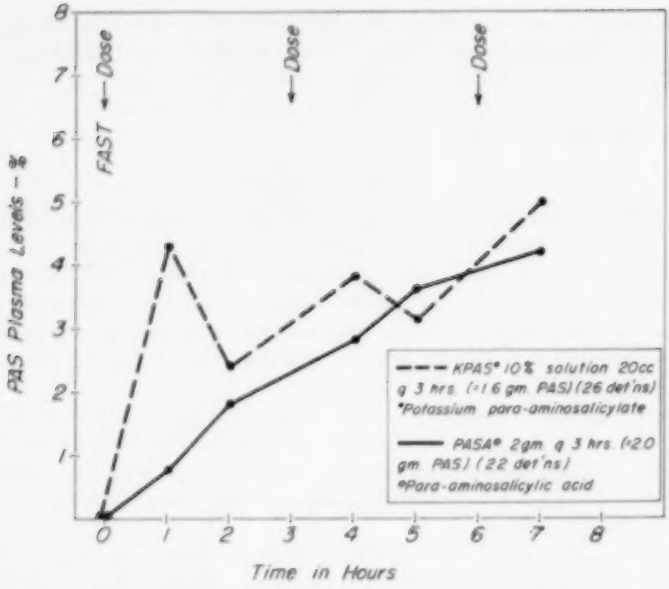

FIG. 2. Average plasma PAS concentrations after 2 gm. doses of indicated compound.

subjects who were taking PAS. Comparative tests were made in 8 subjects who were given first one form of the drug and then the other. Altogether, 178 PAS plasma concentration tests were performed. Two dosage schedules were studied: (*1*) 3 gm. doses of KPAS or PAS every four hours, and (*2*) 2 gm. doses every three hours. The average plasma concentrations obtained with each of these schedules are shown in figures 1 and 2, respectively.

As may be seen, KPAS is more rapidly absorbed and produces adequate blood concentrations when compared with those obtained with PAS. It may be recalled that the 3 gm. (30 ml.) dose of 10 per cent KPAS supplies 2.4 gm. of PAS and the 2 gm. (20 ml.) dose furnishes 1.6 gm. of PAS, whereas the 3 gm. and 2 gm. doses of PAS supply the full amount as PAS. Thus, comparable plasma PAS concentrations were obtained despite the difference in actual PAS administered. This finding suggests that KPAS is also more completely absorbed than is PAS.

DISCUSSION

Ninety-five per cent, or 61 of 64 patients treated, were found to tolerate KPAS in 12 gm. daily doses without difficulty. This finding appears even more remarkable when it is considered that 38 patients, comprising 59 per cent of the entire group, had been intolerant to prior therapy with PAS or NaPAS. Surprisingly enough, the admittedly disagreeable taste of the solution was not a problem, possibly because each patient was told of it prior to institution of therapy. Patients appeared to become accustomed to the taste very rapidly,

and many expressed preference for the liquid form of medication rather than the usual tablets or capsules.

The importance of constant refrigeration and protection from light of solutions of KPAS cannot be overstressed. Some patients who had taken full doses of KPAS for months without difficulty did develop gastrointestinal symptoms when given stale or unrefrigerated solutions. This experience is similar to that which has been encountered during the use of old solutions of other salts of PAS (4).

Aside from the obvious practical importance of general patient acceptance, there are certain additional advantages of the potassium salt over the sodium salt of PAS. One of these is in the treatment of patients who also have cardiac impairment or frank congestive heart failure. Pulmonary tuberculosis is becoming an increasing problem in older men who frequently have concomitant cardiovascular-renal diseases and for whom the administration of large amounts of sodium is contraindicated. In this connection, it may be noted that a daily dose of 12 gm. of NaPAS (8.9 gm. of PAS) contains over 1,300 mg. of sodium, while 16.5 gm. of NaPAS (12 gm. of PAS) provides almost 1,800 mg. of sodium ions. During this study, KPAS was given successfully to 3 patients who were in cardiac failure with fluid retention. It was also administered for several months to 9 patients who exhibited mild degrees of renal impairment, as evidenced by persistently elevated blood urea nitrogen (25 to 35 mg. per 100 ml.) and relatively fixed urine specific gravities (1.010 to 1.018).

Another potential advantage of KPAS lies in the relationship between potassium and nitrogen storage. The work of Cannon, Frazier, and Hughes (5) showed that animals fed supplementary potassium in addition to a basal ration grew at a greater rate, had better appetities, and consumed greater amounts of food than did the control animals. Metabolic studies of the type necessary to evaluate this relationship in man, however, were beyond the scope of this study.

The question of possible potassium toxicity from the use of KPAS may be raised. There was no evidence of its occurrence in these patients, nor has it been noted in the more extensive experience with potassium para-aminobenzoate (KPAB) (1, 2). Observations with oral doses of the latter compound revealed no clinical signs of toxicity following the administration of up to twice the amount of potassium which was given to the patients in the present study. Electrocardiograms have not yet been obtained during KPAS therapy. Tracings taken during KPAB therapy, however, have revealed no abnormalities attributable to potassium excess (6).

The findings of Leaf and associates (7), moreover, indicate that the likelihood of potassium toxicity from oral KPAS, as administered in the present study, is extremely remote. These workers calculate that a normal person having a twenty-four-hour glomerular filtrate volume of 160 liters and a serum potassium concentration of 5 mEq. per liter would filter 750 mEq., or approximately 29 gm., of potassium daily. To increase the normal load requiring excretion significantly more than this, it is estimated that it would be necessary to administer 50 gm. of potassium to the normal subject. As a patient taking 12 gm. of KPAS a day receives only 2.4 gm. of potassium, it is evident that a wide margin of safety is present.

The solution form of KPAS also offers a convenient medium for the "desensitization" of patients who have displayed sensitivity reactions to PAS or any of its salts, including KPAS. According to Korst (8), the incidence of acquired sensitivity reactions to PAS is approximately 2.2 per cent. In the present series, there was one patient who had acquired sensitivity reactions during each of two courses of PAS administered a year earlier, another who manifested sensitivity after taking NaPAS for fourteen days, and one who developed sensitivity after twenty-eight days of KPAS therapy. These patients were successfully "desensitized" by giving the 10 per cent solution of KPAS in doses of 1 drop (equivalent to approximately 7 mg. of KPAS), three times daily, initially, and increasing the amount by 1 drop per dose per day for the first week. The doses were then increased by larger increments until each patient was receiving the full schedule of 30 ml., four times daily, at the end of a month. All three patients have remained on full doses of KPAS following "desensitization" without any untoward reaction.

It should be noted that patients in the present study did not receive KPAS as the sole therapeutic agent. The drug was used along with either streptomycin or isoniazid, or both. No attempt was made to re-determine the efficacy of the various drug combinations or to compare the effects of PAS and KPAS with respect to the disease process. The scope of the present study was confined to an evaluation of the patient acceptance and tolerance of KPAS.

No final statement concerning the optimal dosage of KPAS can be made at this time. Further studies of plasma PAS concentrations using different dosage schedules, comparisons with other salts of PAS, and studies of PAS concentrations in pleural and cerebrospinal fluids are being carried out. The 12 gm. daily dose of KPAS employed in this study produced plasma PAS concentrations comparable to those reached in patients taking a similar amount of PAS, despite the fact that the former drug supplied 20 per cent less free PAS. The plasma PAS concentration studies indicate that prompt absorption and effective plasma concentrations were attained with each of the dosage schedules of KPAS employed. Somewhat higher plasma concentrations were reached on the schedule of 30 ml. four times daily so that it appears to be both more convenient and more efficient than the regimen of 20 ml. six times daily. Certain patients expressed preference for the latter program, however, so that certain individualization seems advisable.

SUMMARY

Potassium para-aminosalicylate (KPAS) was administered in the form of a 10 per cent solution to 64 patients with tuberculosis.

Sixty-one (95 per cent) of the subjects tolerated 12 gm. daily doses of KPAS without difficulty. There were no evidences of potassium toxicity.

Plasma PAS concentration studies indicated that KPAS is more rapidly, and probably more completely, absorbed than is para-aminosalicylic acid (PAS), and that 12 gm. daily doses of KPAS produce PAS plasma concentrations comparable to those obtained with 12 gm. daily doses of PAS.

From these observations, it is concluded that the administration of KPAS, in

the manner detailed herein, offers a superior means of PAS therapy which carries a very high degree of patient tolerance and acceptance.

SUMARIO

Empleo Clínico del Para-Aminosalicilato de Potasio (PASK)

A 64 tuberculosos se les administró pára-aminosalicilato de potasio (PASK) en forma de solución al 10 por ciento.

Sesenta y uno (95 por ciento) de los sujetos toleraron sin dificultad dosis diarias de 12 gm. de PASK. No se observaron signos de intoxicación potásica.

Los estudios de la concentración de PAS en el plasma indicaron que se absorbe el PASP más rápidamente y con toda probabilidad más completamente que el ácido para-aminosalicílico (PAS), y que dosis diarias de 12 gm. de PASK producen concentraciones de PAS en el plasma, comparables a las obtenidas con dosis diarias de 12 gm. de PAS.

De esas observaciones, se deduce que la administración de PASK, en la forma expuesta, ofrece un medio superior para la terapéutica con PAS, que lleva consigo un grado muy alto de tolerancia y recepción de parte del enfermo.

RESUME

Emploi clinique du para-aminosalicylate de potassium (KPAS)

Le para-aminosalicylate de potassium (KPAS) a été administré à 64 tuberculeux sous la forme de solution à 10%.

Soixante-et-un (95%) des sujets ont toléré sans incident des doses quotidiennes de 12 g. de KPAS. Aucun signe d'intolérance au potassium n'a été observé.

L'étude de la concentration du plasma en PAS indiquait que le KPAS est absorbé plus rapidement, et sans doute plus complètement, que l'acide para-aminosalisylique (PAS), et aussi que les dose quotidiennes de 12 g. de KPAS déterminent des concentrations plasmatiques de PAS comparables à celles obtenues avec les doses quotidiennes de 12 g. de PAS.

D'après ces observations, les auteurs concluent que l'administration de KPAS, dans les conditions décrites, constitue le meilleur mode de traitement par le PAS; cette thérapie est extrêmement bien tolérée et acceptée par le malade.

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The writers wish to thank Dr. M. J. Sokoloff and Dr. E. M. Weinberger, Philadelphia, and the Visiting Staff Physicians of the Eagleville Sanatorium for making patients on their respective services available for KPAS therapy. Grateful appreciation is also expressed to Miss Virginia F. Colville and Miss Betty Kane for technical assistance during the course of this study.

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VIABILITY AND MULTIPLICATION OF VACCINES IN IMMUNIZATION AGAINST TUBERCULOSIS[1, 2]

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INTRODUCTION

It is still a matter of controversy whether, in order to be most effective, BCG vaccine should contain the greatest possible number of living bacteria. In the practice of human vaccination, it has been generally accepted that fresh vaccines consisting of live organisms are more desirable than older batches in which part of the organisms may be dead. This assumption is primarily based on the observation that in humans the degree of tuberculin sensitization appears to be proportional to the number of living organisms contained in the vaccine (1). Nevertheless, there is little evidence to show that the degree of acquired antituberculous immunity is equally dependent on this factor.

New interest in this question has been aroused by the observation that exposure to daylight greatly reduces the number of viable organisms and, consequently, the sensitizing properties of BCG vaccine (2–4). If the immunizing properties of such vaccines were likewise reduced by irradiation, this fact would be at variance with claims that bacterial preparations consisting of irradiated suspensions of tubercle bacilli are just as potent immunizing agents as are living vaccines (5–7). At first, it was the purpose of the present study to investigate the influence of light on the immunizing properties of BCG vaccine. While the experiments were under way, a report was published (8) in which it was claimed that the degree of immunization provided by a living vaccine is proportional to the extent of multiplication of the vaccine *in vivo*. The same workers also concluded (9) that certain preparations of killed bacteria or bacterial extracts are able to produce the same degree of immunity as living organisms. Killed vaccines and various bacterial extracts have often been tested as vaccines, with results ranging all the way from virtually no protection to claims that they are superior to BCG or other living vaccines. The literature contains too many papers on this subject to permit a review in the present report. Because of the contradictory nature of some of these reports, the present study was broadened into an investigation of the role of viability and multiplication of vaccines in immunization against tuberculosis. The experiments were performed, using mice. A report on similar experiments in guinea pigs will be published shortly (10).

MATERIALS AND METHODS

Animals: Male mice of the CF_1 strain, received from Carworth Farms, New City, New York, were used. The mice were fed a standard diet of pellets and water and housed in

[1] From the Division of Tuberculosis, The Public Health Research Institute of The City of New York, Inc., New York, N. Y.

[2] This study was carried out under the terms of a cooperative agreement between this Institute and the Field Research Branch, Division of Chronic Diseases and Tuberculosis, U. S. Public Health Service.

solid-wall metal cages in groups not exceeding 10 animals. They were weighed twice weekly. All dead mice were autopsied and their organs were carefully inspected. When characteristic lesions were not clearly seen, Ziehl-Neelsen-stained smears and histologic sections were made to ascertain the presence of acid-fast bacteria and tuberculous tissue reactions.

Vaccines: The bacterial vaccines used were either dilutions of one-week cultures grown in liquid Tween®-albumin medium (11) or finely ground suspensions in saline or fresh medium of two-week surface cultures from a modified Lockemann medium (12). The potency was determined by measuring the opacity of the suspension in a Coleman Senior spectrophotometer, by determining the bacterial weight, and/or by plate counts on solid oleic-acid-albumin medium (13). The mice were vaccinated by the intravenous or the intraperitoneal route, as indicated below.

Vaccines were prepared from the following three strains: *BCG "Phipps,"* obtained through the courtesy of Dr. R. J. Dubos of The Rockefeller Institute for Medical Research, New York, New York; *H37Ra*, an avirulent mutant of the human strain H37Rv; and *M. phlei*, both obtained through the courtesy of Mr. W. Steenken, The Trudeau Laboratory, Saranac Lake, New York.

Various means were employed for inactivating the vaccines, as follows:

Heat: The final bacterial suspensions were sealed in a tube and immersed in a water bath of 70°C. for forty-five minutes.

Phenol: The method of Dubos and associates (9) was used exactly as described by these writers.

Irradiation: The procedure is described in detail in the foregoing paper (14).

Challenge infections: All mice were challenged intravenously with 0.1 ml. of a five-day Tween®-albumin culture of H37Rv of desired strength. Previous experience has shown that there is proportionality between the number and age of bacteria injected and the severity of the infection they produce in mice (15). The methods used for standardizing the challenge dose were the same as those previously described.

Evaluation of immunity: The degree of acquired immunity was measured by comparing the survival times after challenge of vaccinated groups with the survival of nonvaccinated control mice of the same age, weight, and sex. By determining the ratio of the median survival time of a vaccinated group to its control group, a value was obtained which was termed "vaccination index." This quotient gives a convenient estimation of the relative degree of immunity.

EXPERIMENTAL

Vaccination Experiments with Irradiated Vaccines

Two experiments were carried out, the results of which are summarized in tables 1 and 2. In the first experiment (table 1), groups of 10 mice each were injected intravenously with suspensions of Tween®-albumin–cultured BCG, irradiated for various lengths of time. Twenty-two days later, the mice were challenged intravenously. The challenge dose chosen was a heavy one which caused the death of all controls within eighteen to twenty-two days. The control mice were of the same age as the vaccinated mice. During the vaccination period, they had been kept under identical conditions as the vaccinated groups. All mice were challenged at the same time.

It may be seen from table 1 that the degree of immunity conferred by vaccination was proportional to the number of living cells in the vaccine. Due to a technical error, no plate count of the irradiated vaccines was made. The fraction of bacteria which survived after exposure to the sunlamp was estimated in this experiment (table 1) on the basis of the plate counts shown in table 2. These counts are consistent with the results of repeated irradiation experiments with BCG not reported in the present paper.

TABLE 1

EFFECT OF IRRADIATION AND CONSEQUENT LOWERED VIABILITY ON THE IMMUNIZING CAPACITY OF BCG

Number of Mice per Group	Number of Minutes Vaccine Was Irradiated	Estimated Fraction of Surviving Organisms	Survival Times of Mice After Challenge Infection	Average Survival Time	Vaccination Index
			days	*days*	
10	0	1/1	18, 91, 102, 106, 129, 147, 150, 171, 181, 201	129.6	6.7
9*	4	5/8	28, 33, 90, 90, 101, 102, 127, 149, 186	100.6	5.2
10	8	1/13	18, 29, 67, 84, 87, 87, 94, 130, 194, 200	108.0	5.6
9*	12	1/40	19, 21, 22, 35, 42, 70, 131, 134, 155	69.9	3.6
10	16	1/166	20, 20, 20, 21, 21, 28, 35, 67, 83, 110	42.5	2.2
10	24	1/18,600	22, 24, 24, 28, 28, 42, 49, 59, 67, 114	45.7	2.3
10	32	0	20, 21, 21, 23, 23, 24, 33, 34, 71, 83	35.3	1.8
10	Infection control		18, 18, 19, 19, 19, 19, 20, 20, 20, 22	19.4	—

* One mouse died accidentally before challenge.

A second vaccination experiment was then performed which was essentially similar. There were 15 mice in each group and the challenge dose chosen was smaller. This was done because it has been observed many times that a definite break occurs in a survival curve when it extends over more than four weeks. The curve flattens out to a plateau-like stretch, during which time few animals die, and only at a later period does the survival curve resume its original downward trend. Curves of this type have been published by other workers and in previous papers (15, 16).

In the present experiment, the milder infection allowed some of the animals to survive for more than four weeks. This eliminated a factor which might permit the survival curve of the vaccinated groups to appear disproportionately more favorable than the controls, because the effects of vaccination would most likely carry the immunized mice over into the period where the survival curve turns flat even without vaccination.

The data pertaining to this experiment are listed in table 2. In this experiment, plate counts were made and the actual fraction of bacteria surviving exposure to the sunlamp was determined. This table also lists dilution controls. The latter groups of mice were vaccinated with vaccines made from the original BCG suspension used for irradiation, but diluted with saline by factors estimated to fall within the range of the actual reductions caused by the various periods of irradiation. While the estimated and calculated reduction factors were not exactly the same, they lay within a reasonable range and the results are comparable.

Both irradiation and dilution had a clearly weakening effect on the immunizing power of vaccines. The proportion of dead bacilli in the irradiated batches seemed to contribute little, if anything, to the potency of the vaccine. Furthermore, it is evident from a comparison of the results in tables 1 and 2 that the relative value

TABLE 2

EFFECT OF IRRADIATION AND CONSEQUENT LOWERED VIABILITY ON THE IMMUNIZING CAPACITY OF BCG

Number of Mice per Group	Number of Minutes Vaccine Was Irradiated	Number of Viable Bacterial Units per 0.1 Ml. ($\times 10^6$)	Calculated Fraction of Surviving Organisms	Survival Times of Mice After Challenge Infection	Median Survival Time	Vaccination Index
				days	*days*	
15	0	8	$\frac{1}{1}$	10, 15, 53, 76, 104, 115, 116, 131, 152, 156, S*, S, S, S, S	116	4.8
15	4	5	$\frac{5}{8}$	8, 63, 104, 108, 138, 143, 146, S, S, S, S, S, S, S	146	6.0
15	8	0.6	$\frac{1}{13}$	29, 35, 57, 63, 79, 85, 110, 132, 136, 137, 139, 162, 169, S, S	87	3.6
15	12	0.2	$\frac{1}{40}$	13, 18, 24, 67, 69, 85, 87, 87, 123, 133, 136, 169, S, S, S	87	3.6
15	16	0.048	$\frac{1}{166}$	23, 31, 48, 49, 59, 77, 80, 83, 126, 127, 130, 133, 133, 156, S	80	3.3
15	24	0.00043	$\frac{1}{18,600}$	18, 22, 24, 29, 36, 53, 63, 66, 78, 85, 89, 91, 121, 122, S	63	2.6
15	32	0.0	0	21, 25, 29, 30, 30, 31, 60, 66, 74, 76, 78, 94, 95, 108, 129	60	2.5
15	Dilution control I		$\frac{1}{100}$	16, 27, 32, 42, 49, 77, 92, 94, 96, 116, 116, 127, 133, 139, 152	92	3.8
11†	Dilution control II		$\frac{1}{1,000}$	23, 23, 23, 31, 45, 53, 60, 98, 103, 141, 251	53	2.2
15	Infection control			18, 21, 21, 22, 22, 23, 24, 25, 31, 36, 48, 63, 70, 123, 155	24	—

* S indicates the mouse was sacrificed 285 days after infection.

† Four mice of this group died accidentally before challenge.

of the vaccine (vaccination index) was independent of the challenge dose. For practical considerations, however, weak challenge doses combined with potent vaccines are not very convenient when survival time is taken as a criterion for the efficacy of vaccination.

Thus far, the vaccines had been given intravenously. With large numbers of animals, intraperitoneal injections would be less laborious, and a test was therefore made on a significant number of mice to compare the two methods. Two groups of 60 mice each were injected by the intravenous and the intraperitoneal routes, respectively, with the same dose of 0.1 ml. of a Tween®-albumin–BCG culture (approximately 10^5 organisms). Three weeks later, they were challenged together with a control group of 60 mice of the same age and weight. The survival curves of the three groups are shown in figure 1.

For reasons not revealed by the present experiments, the same vaccine given by the intraperitoneal route afforded a significantly higher degree of protection than was achieved with intravenous vaccination.

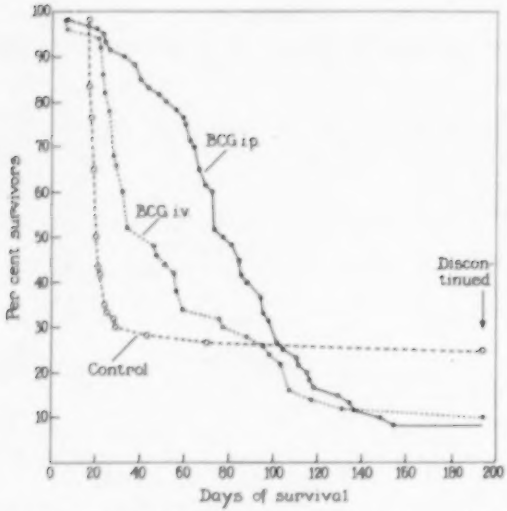

FIG. 1. Comparative effects of intravenous and intraperitoneal BCG vaccination in mice (60 mice per group, challenged three weeks after vaccination).

Influence of Isoniazid Therapy on the Effects of Vaccination

It appeared from the preceding experiments that the degree of protection conferred upon mice by BCG was proportional to the number of living bacteria present in the vaccine. It did not seem to matter whether the vaccine consisted of a mixture of living and dead organisms or whether it contained only living BCG, as long as the number of living bacilli was the same. In these experiments, the variation in the number of living cells had been effected by irradiation or dilution of a fresh vaccine. Another method of reducing the proportion of live BCG organisms is to prevent them, by chemotherapy, from multiplying *in vivo*.

Dubos, Pierce, and Schaefer have recently used this apprach (8). They concluded from their data that isoniazid therapy which interfered with the multiplication of a vaccine consisting of the attenuated strain of *M. tuberculosis*, R1Rv, also reduced the immunizing power of the vaccine. Chemotherapy did not eradicate R1Rv completely, however, and, when sufficient time was allowed to elapse between the cessation of therapy and the challenge infection, protection was again detectable.

The present experiment was planned as follows:

A total of 330 mice was used, eleven groups of 30 mice each. All animals were of the same age and were caged on the same day. They were vaccinated intraperitoneally on different days with 0.1 ml. of five-day Tween®-albumin cultures of BCG, photometrically adjusted to equal density (5×10^6 bacilli per ml.). The vaccination dates were so chosen that on a particular day one group had been vaccinated for three days, one group had received its vaccine six days before, one group had been vaccinated for twelve days, and one for twenty-

TABLE 3

THE EFFECT OF ISONIAZID ON BCG VACCINATION IN MICE

Group Number (30 Mice per Group)	Nature of Vaccine	Isoniazid Groups		Control Groups	Median Survival Time	Vaccination Index
		Number of Days Vaccinated Before Inception of Drug Treatment	Total Number of Days Vaccinated Before Challenge	Number of Days Vaccinated Before Challenge		
					days	
1	Living BCG	24	41		163	4.0
2	Living BCG	12	29		130	3.2
3	Living BCG	6	23		134	3.3
4	Living BCG	3	20		126	3.1
5	Living BCG			41	171	4.2
6	Living BCG			24	134	3.3
7	Living BCG			13	115	2.8
8	Living BCG			6	133	3.2
9	Living BCG			3	79	1.9
10	Heat-killed BCG			3	77	1.9
11	Infection control			0	41	—

four. On the chosen day, all of these groups were put on isoniazid.[3] The drug was given as a 0.1 per cent addition to a powdered standard diet, corresponding to an isoniazid intake of about 4 mg. per day per mouse. This is a highly effective dose, as shown by numerous chemotherapeutic experiments. Isoniazid treatment was continued for fourteen days, and the mice were then returned to a drug-free diet. Three days later, they were challenged. On this same date, seven groups were also challenged with the same dose of virulent bacilli as follows (group numbers as shown in table 3): One group of mice vaccinated three days prior to challenge (*Group 9*); one group vaccinated six days before challenge (*Group 8*); a group vaccinated thirteen days before infection (*Group 7*); a group vaccinated twenty-four days prior to infection (*Group 6*); one group vaccinated forty-one days before challenge (*Group 5*); one group vaccinated three days before infection with a tenfold concentrated suspension of heat-killed BCG bacilli (*Group 10*); a nonvaccinated control group (*Group 11*).

For better comprehension of the experimental plan, the various procedures are tabulated in table 3, which also shows the vaccination index obtained with each group.

It may be seen that for each of the nonisoniazid-treated vaccine groups, i.e. *Groups 6* to *9*, there was a corresponding group of mice which had been vaccinated for an equal length of time before the inception of the two-week chemotherapy period introduced before challenge. *Groups 5* to *7* served as controls, covering approximately the total pre-challenge period of *Groups 1* to *4*. The heat-killed vaccine was added because it was thought that its effect might be roughly comparable to that of the BCG vaccine, the multiplication of which was interrupted by isoniazid after three days. The seventy-two-hour interval between cessation of therapy and challenge served to eliminate from the body fluids of the treated animals all possible traces of isoniazid which might interfere with the challenge dose.

The survival times of all of the 330 animals are illustrated in figure 2. The

[3] Received through the courtesy of E. R. Squibb & Sons, New York, N. Y.

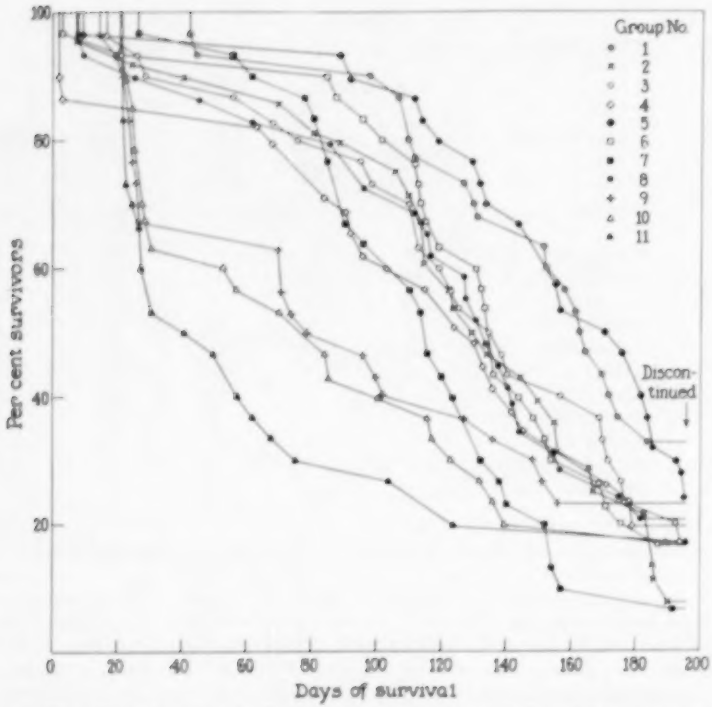

FIG. 2. The effect of isoniazid given for various lengths of time to BCG-vaccinated mice prior to the challenge infection (30 mice per group). The details of this experiment are explained in the text and summarized in table 3.

challenge dose chosen was a mild one which resulted in a more chronic type of disease. Several facts are evident from this figure. The survival curves of *Groups 1* to *8* fell closely together. The relatively small differences which existed between these groups were correlated with the total length of the vaccination period before challenge. While the groups vaccinated longest before infection had the best degree of protection, this was entirely independent of whether isoniazid had been given or not.

There is a clearly distinct intermediate group between the infection control group and *Groups 1* to *8*. This category consists of *Groups 9* and *10*. The 60 animals in these groups had considerably less immunity than the rest of the vaccinated mice; however, they still had a longer survival time than the nonvaccinated control group. The two curves of *Groups 9* and *10* are almost identical.

Vaccination with a living vaccine was thus tantamount to the effects of a more concentrated heat-killed vaccine when the challenge infection was given only three days after vaccination. The crucial rise in immunity occurred between the third and the sixth days after vaccination, when immunity reached a level which increased only slightly with time.

TABLE 4

THE EFFECT OF ISONIAZID ON BCG VACCINATION IN MICE

Group Number (20 Mice per Group)	Prechallenge Treatment	Total Length of Vaccination Period	Survival Times of Mice After Challenge Infection	Median Survival Time	Vaccination Index
		days	*days*	*days*	
1	Mice vaccinated 3 days before receiving isoniazid for 14 days	17	19, 26, 52, 73, 74, 80, 80, 87, 92, 95, 104, 107, 108, 108, 8*, 8, 8, 8, 8, 8	95	4.1
2	Mice vaccinated and isoniazid treatment started on same day; treatment continued for 2 weeks	14	19, 20, 23, 27, 31, 52, 52, 70, 76, 81, 82, 83, 85, 87, 94, 105, 105, 105, 8, 8	81	3.5
3	Mice vaccinated 3 days before challenge; no isoniazid treatment	3	18, 18, 20, 20, 20, 22, 23, 23, 24, 24, 37, 42, 47, 49, 62, 62, 63, 66, 76, 108	24	1.0
4	BCG control: vaccinated 17 days before challenge; no isoniazid treatment	17	17, 20, 22, 62, 63, 64, 75, 80, 82, 85, 87, 90, 93, 8, 8, 8, 8, 8, 8, 8	85	3.7
5	Isoniazid nonvaccinated control: mice treated with isoniazid for 2-week period 3 days after challenge infection	—	63, 94, 8, 8, 8, 8, 8, 8, 8, 8, 8, 8, 8, 8, 8, 8, 8, 8, 8, 8	108*	—
6	Infection control†	—	19, 19, 20, 20, 20, 21, 21, 21, 22, 23, 26, 30, 38, 51, 58, 63, 70, 74, 76, 8	23	—

* Sacrificed after 108 days.

† These mice were given isoniazid for 2 weeks before they were infected.

If isoniazid interferes with the immunizing properties of BCG, this should be evident by a comparison of *Groups 4* and *9*, which would be similar to one another. Instead, the survival curve of *Group 4* is comparable with any of the curves of *Groups 1* to *8* and quite different from the curve of *Group 9*. The experiment was discontinued 200 days after challenge and the remaining animals of each group were sacrificed. The sacrificed animals were autopsied. They all had tuberculous lesions typical of this chronic type of disease.[4]

It could be argued that, as three days were allowed to elapse between cessation of therapy and challenge infection, the BCG organisms had an opportunity to start multiplying again and reach the critical level necessary to produce immunity. The following experiment was done to test this possibility.

Twenty mice were vaccinated intraperitoneally with BCG.[5] Three days after vaccination they were treated with isoniazid for two weeks and challenged on the same day on which isoniazid was discontinued. A second group was vaccinated and challenged three days later. A third group was started on isoniazid a few hours before it was vaccinated.

[4] An *in vitro* test showed that the strain of BCG was susceptible to 0.01 γ of isoniazid per ml.

[5] Approximately 2×10^6 viable organisms per dose.

After two weeks, treatment was discontinued, and the mice were challenged the same day. One last group of animals was infected with the usual challenge dose of H37Rv. After three days, isoniazid treatment was started and continued for two weeks. The mice were then observed without further treatment. This group was included to illustrate the fact that isoniazid therapy in this dosage is highly effective. The experiment was so arranged that all vaccine groups and the infection controls were challenged on the same day and with the same bacterial suspension, while comparable BCG cultures were used for the various vaccination groups. Prior to being challenged, the infection controls received isoniazid for the same period of time as the vaccine groups.

The elements of this experiment and the resultant survival times are tabulated in table 4. The results are similar to the previous ones. The seeming difference between the complete lack of immunity shown for the three-day vaccination period in table 4 and the limited immunity shown for this same group in table 3 is accounted for by the use of a heavier vaccination dose and a much lighter challenge dose in the experiment in table 3. It was shown that the lapse of three days between cessation of treatment and challenge had been of no consequence in the previous experiment. Even in *Group 2* (table 4), in which there was no delay between isoniazid treatment and vaccination and in which the drug was given during the entire pre-challenge period, there was hardly a reduction in immunity. Moreover, in this experiment the mice were given a severe challenge dose.

The results suggest that bacterial multiplication is not an essential factor in this type of vaccination. This conclusion is based on the assumption that isoniazid inhibits multiplication of BCG in the mouse.

While it has been shown in the present experiments that the strain of BCG used was highly susceptible to isoniazid *in vitro*, it has not been demonstrated directly that isoniazid inhibits its multiplication *in vivo* as well. However, it seems reasonable to assume that it does so. The dose of 0.1 per cent of isoniazid in the diet used in the present experiments is at least 500 times greater than the minimum dose which in this laboratory has been found to be effective therapy for mice infected with large numbers of virulent strains of tubercle bacilli of human or bovine origin.

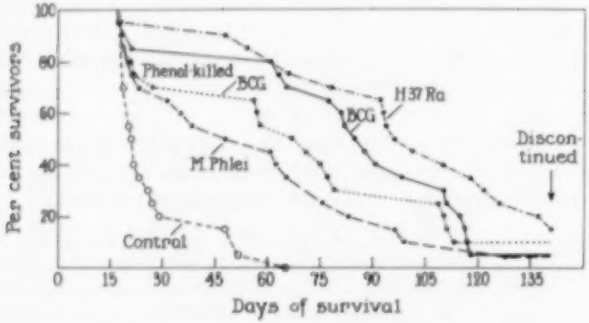

FIG. 3. Comparative effects of various antituberculous vaccines in mice (20 animals per group, challenged three weeks after vaccination).

Vaccination with Nonmultiplying and Killed Vaccines

If bacterial multiplication of the vaccine is not essential in antituberculous vaccination, similar protection should be afforded by certain nonmultiplying vaccines or, perhaps, by preparations consisting of killed mycobacteria. In figure 3 are summarized experiments in which mice were vaccinated with equal suspensions (0.075 mg. wet weight of two-week-old surface cultures) of living organisms of the BCG and the H37Ra strains of *M. tuberculosis* as well as of *M. phlei*. These vaccines were compared with equal suspensions of phenol-killed BCG cultures.

The results showed an increasing efficacy of equal amounts of the four vaccines in the following order: *M. phlei* (living, presumably nonmultiplying *in vivo*); phenol-treated BCG (dead, nonmultiplying); BCG (living, multiplying); H37Ra (living, nonmultiplying).

As H37Ra does not multiply in mice, the results should be even clearer with smaller vaccine doses. An experiment was therefore planned in which the two living vaccines, consisting of multiplying (BCG) and nonmultiplying (H37Ra) organisms, were compared in various doses.

Two five-day-old Tween®-albumin cultures of BCG and of H37Ra were brought to equal optical density (41 per cent light transmittance at 550λ) and the number of viable cells determined by plate counts. Of these suspensions, serial dilutions were made in water containing 0.5 per cent bovine albumin, and groups of 25 mice each were vaccinated intraperitoneally with 0.1 ml. of the undiluted suspension and 10-, 100- and 1,000-fold dilutions thereof. According to the results of the plate counts of the two bacterial suspensions, this

TABLE 5

COMPARATIVE IMMUNIZING EFFECTS OF VARIOUS DOSES OF VACCINES CONSISTING OF VIABLE BACTERIAL SUSPENSIONS OF EQUAL STRENGTH OF BCG AND H37Ra

Group Number (25 Mice per Group)	Vaccine and Dose*	Individual Survival Times After Challenge Infection†	Number of Survivors After 70 Days
		days	
1	BCG undiluted	13, 26, 34, 36, 42, 48, 66	18
2	H37Ra undiluted	6, 10, 30, 47, 69	20
3	BCG 1:10	18, 19, 21, 22, 23, 24, 29, 69, 69	16
4	H37Ra 1:10	20, 32, 40, 43, 44, 50, 61, 69	17
5	BCG 1:100	8, 17, 18, 18, 19, 19, 22, 23, 27, 29, 34, 34, 36, 36	11
6	H37Ra 1:100	9, 19, 26, 29, 32, 36, 59	18
7	BCG 1:1,000	18, 19, 19, 20, 20, 21, 22, 23, 23, 26, 28, 32, 39, 39, 58, 59, 59, 60, 60, 68, 69	4
8	H37Ra 1:1,000	18, 18, 18, 19, 20, 20, 20, 23, 24, 25, 26, 27, 29, 34, 40, 42, 67, 67	7
9	Nonvaccinated controls	17, 17, 18, 19, 19, 19, 19, 19, 19, 19, 19, 20, 20, 20, 20, 20, 22, 23, 23, 23, 27, 28, 30	2

* The undiluted vaccines consisted of suspensions containing 1.7×10^6 viable bacterial units per dose.

† This column lists the individual survival times (in days) of the mice which died from tuberculosis during the observation period of 70 days. The experiment was discontinued after 70 days.

corresponds to vaccine doses ranging from 1.7×10^3 up to 1,000 times this concentration of bacterial units per 0.1 ml. Three weeks later, the 200 vaccinated mice and 25 control mice of the same age were challenged intravenously.

The results are summarized in table 5 and indicate the superiority of the H37Ra vaccine over BCG. It is noteworthy that even as small a vaccine dose as 1,700 bacterial units of the nonmultiplying H37Ra strain conferred some degree of immunity. As in the previous experiments, immunity became more evident with increasing doses of vaccine. Consistently, the H37Ra vaccine was superior to BCG.

In order to ascertain whether BCG really multiplies *in vivo*, whereas H37Ra does not, a number of additional mice vaccinated with each strain were killed at different intervals. Their spleens were ground and three tubes of Löwenstein medium were inoculated with the pulp of each organ. The cultures were inspected five weeks after inoculation and the results are shown in table 6. Moreover, plate counts were made of the pooled suspensions of spleen, liver, and lungs. As was expected, and in confirmation of the findings of Pierce, Dubos, and Schaefer (17), BCG multiplied in the mice, whereas H37Ra did not. Three weeks after vaccination, no organisms of the H37Ra strain could be found in the spleens of the mice inoculated with the smallest dose, whereas the corresponding BCG group showed an abundance of bacteria.

Duration of Acquired Immunity in Mice

In most experiments designed to study the effects of vaccination, the animals are challenged in a relatively short time after they have been vaccinated, usually

TABLE 6

BACILLI OF THE H37Ra AND BCG STRAINS RECOVERED FROM MOUSE ORGANS AFTER VARIOUS INTERVALS OF TIME

Strain	Dose	Bacteria Recovered from Spleens; Bacterial Growth on Löwenstein Medium* and Time Interval at Which Mice Were Sacrificed After Vaccination			Number of Colonies Recovered from Pooled Organs† ($\times 10^6$) 5 Weeks
		3 Weeks	5 Weeks	7 Weeks	
H37Ra	Undiluted	+++	++	+	3
H37Ra	1:10	+++	+	0	0.08
H37Ra	1:100	++	0	0	0
H37Ra	1:1,000	0	0	0	0
BCG	Undiluted	+++	+++	+++	231
BCG	1:10	+++	++	+++	112
BCG	1:100	+++	++	++	89
BCG	1:1,000	+++	++	++	63

* The growth intensity is indicated in a scale ranging from 0 to +++ as follows: 0 = no visible colonies; + = 1 to 5 colonies; ++ = 6 to 15 colonies; +++ = more than 15 colonies.

† Lungs, livers, and spleens were aseptically removed and ground in a Virtis homogenizer. Serial dilutions were made from the pooled, ground organs and plated out on oleic-acid–albumin medium. The numbers represent average values from 3 mice each.

within three to five weeks. It is assumed from analogy with experience in other fields that at this time immunity has fully developed. This assumption was confirmed in the present study.

It has been shown that, within a period of three to six days after vaccination, a conspicuous degree of resistance is acquired and that a further extension of the pre-challenge period adds but little to the level of immunity. However, little is known about the duration of acquired immunity. Wells and Wylie (18) have shown in guinea pigs (6 animals per group) that animals vaccinated with 2 mg. (wet weight?) of BCG lost their skin sensitivity to tuberculin within approximately seven months after vaccination. When challenged at this time, their resistance was less than it had been in a comparable group two weeks after vaccination. Six months after disappearance of skin sensitivity (or approximately thirteen months after vaccination), such guinea pigs did not have any noticeable degree of acquired immunity left.

In the present studies, 240 mice were vaccinated intraperitoneally at the same

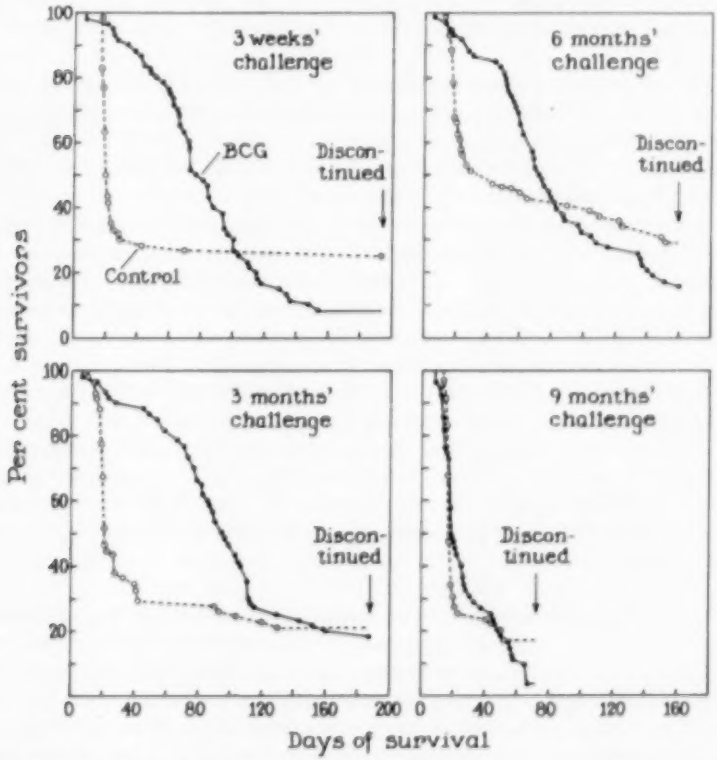

FIG. 4. The effects of BCG vaccination in mice challenged three weeks, three months, six months, and nine months after vaccination (60 mice per group).

TABLE 7

COMPARISON BETWEEN THE MEDIAN SURVIVAL TIMES OF VACCINATED GROUPS OF MICE CHALLENGED AT INTERVALS RANGING FROM THREE WEEKS TO NINE MONTHS AFTER VACCINATION

Interval Between Vaccination and Challenge	Median Survival Time		Vaccination Index
	Nonvaccinated	Vaccinated	
months	*days*		
0.75	20	77	3.85
3	21	95	4.52
6	40	83	2.07
9	18	19	1.05

time with 0.1 ml. of a five-day Tween®-albumin culture of BCG (approximately 10^5 infectious units). They were caged and housed in a room in which there were no infected animals. An equal number of control mice were caged at the same time. Groups of 60 vaccinated and 60 nonvaccinated mice were challenged three weeks, three months, six months, and nine months, respectively, after vaccination.

The results are shown in four pairs of survival curves (figure 4). It may be seen from these figures that the highest level of immunity was reached between three weeks (or less) and three months after vaccination. At six months, it was slightly lower, and at nine months there was very little persisting immunity.

The waxing and waning of resistance can also be seen by comparing the median survival times and their ratios in the different groups (table 7). It will be noticed that the severity of the challenge dose was the same in the three-week and three-month groups. The six-month group was challenged with a slightly less virulent dose, and the nine-month group challenge dose was again somewhat more severe. These variations occurred inadvertently. However, if the vaccination indices are determined, the results are comparable.

Another interesting feature of the curves in figure 4 is the fact that, in every pair of vaccinated mice and nonvaccinated controls, the two survival curves cross each other at a certain point. This usually occurred after approximately 70 to 80 per cent of the mice in each group had died. Thus, at this point, the life expectancy of the remaining mice became smaller for the vaccinated mice than for the nonvaccinated infected controls. This observation will be discussed later.

DISCUSSION

As long as a specific laboratory test is not available, the only way of measuring immunity in tuberculosis is by assessing an animal's resistance to infection. This can be done by various methods, such as sacrificing experimental animals at various times and estimating the number of viable bacilli in one or several organs (8); comparing the size, number, and extent of gross tuberculous lesions in various sites (19); and by allowing the infection to take its course and recording the length of the survival times.

In the present study, the survival-time method was chosen because it was be-

lieved that the results thus obtained are less equivocal than the ones obtained with any other method.

A vaccine has to be regarded as having some beneficiary effect if, by its action, the lifespan of an experimental animal afflicted with a fatal disease is significantly extended. The measure of significant extensions of survival times thus represents the most comprehensive index of immunity. To be sure, bacterial counts and estimation of gross pathologic lesions provide valuable information on the mechanisms of vaccination; but they cannot, in the present writers' view, be substituted for the more direct and simpler method of comparing the survival times in vaccinated and control animals.

It may be recalled that the experiments reported in the foregoing paper (14) indicate that not under every circumstance is there a parallel between the number of bacteria grown *in vitro* and the severity of an infection caused by an equal number of organisms of the same bacterial strain. In addition, the method of comparing survival times in vaccinated and control animals permits the use of larger animal groups, thus increasing the statistical significance of the results. The importance of this last point cannot be overestimated.

One of the consequences of measuring immunity by the degree of resistance against infection is the dependence of the experimental results on the nature of the challenge infection. It has previously been pointed out that there are various factors which determine the severity of the resulting disease. These include the virulence of the bacterial strain, the age of the culture, the size of the challenge dose, the genetic susceptibility of the animal, and a number of so-called unspecific factors (20). Despite all this, the present experiments show that the *relative* degree of immunity (vaccination index) resulting from a particular vaccine remains the same, independent of the severity of the challenge dose.

Of the vaccines compared in the present experiments, living organisms provided better immunity than comparable killed preparations. This is in accordance with the general conclusions reached by many previous investigators. Recently, however, it has been postulated anew by several writers that bacterial cultures killed by irradiation, formaldehyde, or phenol treatment compare favorably with living vaccines (5–7, 9, 21, 22). Formol-treated preparations have not been included in the present experiments, but neither irradiated nor phenol-killed bacilli produced effects comparable with the results obtained with living bacterial suspensions of the same strain. Vaccines irradiated with various doses of light provided a degree of immunity exactly proportional to the number of surviving bacteria. The killed bacteria present in these partially inactivated preparations did not have any noticeable immunizing effect. Similar results were obtained in guinea pigs by Seagle, Karlson, and Feldman (23).

As has been shown by many previous writers, some degree of immunity occurs after vaccination with relatively large doses of killed organisms. This is confirmed in the present experiments, but the immunity achieved by use of such preparations is low and does not stand comparison with the vaccination effect of a comparable dose of living organisms of the same strain. A similar low level of resistance has been found after vaccinating mice with suspensions of *M. phlei*.

While there is in the present results a definite difference between living and dead vaccines, no such distinction could be found between vaccine preparations consisting of variants of *M. tuberculosis* capable or incapable of multiplication *in vivo*. Pierce, Dubos, and Schaefer (17) have shown that BCG multiplies in mice, whereas bacteria of the avirulent mutant H37Ra fail to do so. These investigators conclude (8) that BCG is also a more potent vaccine than H37Ra, and they ascribe the superiority of the former to the fact that it multiplies in the mouse. The findings set forth in the present paper are at variance with these conclusions. In all of the present experiments, suspensions of living H37Ra bacilli were better immunizing agents than equal numbers of BCG. The differences were small but consistent.

It is to be expected from analogy with immunization studies in other fields that a systematic search would reveal further differences between the immunizing capacities of various nonpathogenic mycobacteria. So far, however, the present results indicate that bacterial multiplication *in vivo* is not an essential condition for a vaccine to be effective. This conclusion is further supported by the isoniazid experiments reported above, which are again in contradiction to the results of Dubos, Pierce, and Schaefer (8), as are the findings on the comparative value of intravenous versus intraperitoneal vaccination.

It is difficult to find an explanation for the consistent disagreement between the experimental results of the present study and the observations of Dubos, Pierce, and Schaefer. Only a few obvious points may be mentioned and discussed. In the two experiments of Dubos and co-workers (8), in which living vaccines of H37Ra and BCG were compared and survival times were used to measure immunity, the actual size of the doses of vaccine used for immunization was not reported. The dose was indicated merely by a dilution factor of not otherwise defined bacterial cultures (table 1 of their paper). It is difficult to judge, therefore, whether the doses are strictly comparable in terms of content of living organisms with the doses used in the present experiments. In their experiments, when various doses of BCG were compared (table 2 of their paper), there was no significant difference between the survival of mice vaccinated with two suspensions of the same strain which varied one hundred times in strength. A similar lack of correlation between vaccine dose and immune response was evident when phenol-killed H37Ra over a twenty-fold range of dosage did not show any difference in immunization effects (table 3 of a subsequent paper by Dubos and co-workers (9)). According to the experience of the present writers and also the conclusions reached by Dubos and associates, such differences should be noticeable, especially because, with BCG, sufficient time for *in vivo* multiplication was allowed to elapse between the vaccination and the challenge dates.

In the second paper (9), Dubos and associates have further proposed that the difference they observed in immunizing capacity between living H37Ra and BCG is essentially quantitative, due to multiplication of BCG *in vivo*. According to this hypothesis, a critical level of bacterial protoplasm is sufficient to confer immunity regardless of whether the bacilli are living or dead. Several results of the experiments reported in the present communication tend to dispute this hypothesis:

Although phenol-killed BCG was a less effective immunizing agent than living BCG, a vaccine of living H37Ra of the same cell concentration as the killed and living BCG produced an immunity even greater than that of the living BCG. Furthermore, in the lowest of concentrations, far below the usual immunizing dose (and far below the limiting effective dose of phenol-killed H37Ra shown by Dubos and associates), H37Ra still showed immunizing properties comparable to those of BCG. When isoniazid was used to inhibit the multiplication of BCG *in vivo* by administration throughout the period of vaccination, a high level of immunity resulted, far superior to that obtained for an equivalent amount of phenol-killed BCG.

Thus, even when equivalent amounts have been used, the viability of the vaccine seems to be the chief factor in conferring immunity.

Some of the inconsistencies between the present results and the observations of Dubos and associates may be found in the fact that, whenever in their experiments survival time was used as a criterion of immunity, the mice were challenged with huge doses of virulent bacilli; whereas, when immunity was estimated by the number of tubercle bacilli recovered from various organs, the challenge dose was 10,000 times smaller. The vaccine doses, on the other hand, always remained the same and were relatively small. In their survival experiments, vaccination effects could well be overlooked by making the ratio between vaccine and challenge dose too unfavorable. Moreover, the use of different strains of virulent bacilli and mice in their studies and in the present investigation might account for some of the differences in the results.

The results reported in table 5 of the present paper clearly demonstrate the dependence on dosage of the degree of protection reached with various vaccines. Likewise, the results show that living H37Ra produced better immunity than BCG. The same distinction between the immunizing properties of the two strains has been found in guinea pig experiments (10). Other workers have reported similar favorable effects of living H37Ra vaccines (24, 25).

While this manuscript was in preparation, a paper appeared by Mackaness, Smith, and Wells (26) in which they showed that, in macrophages surviving *in vitro*, H37Ra multiplied slowly while BCG failed to do so. The data reported in table 6 show that no such reversal of what has been generally found with regard to the multiplication rate of the two strains occurred in the present experiments.

The immunity provided by BCG was not only dependent on the size of the vaccination dose, but also on the length of time which elapsed between vaccination and challenge infection. With the vaccine doses used, a steep rise of acquired resistance occurred between the third and the sixth days after vaccination. Between three and twelve weeks after BCG was given, the highest level of immunity was reached. From then on it decreased and became insignificant if the mice were challenged nine months after immunization. These findings appear noteworthy in view of their possible application to the practice used in human vaccination with BCG.

In mice, the relative degree of antituberculous immunity acquired by vaccination is clearly dependent on the vaccine dose as well as on unknown intrinsic qualities of the strain used for the preparation of the vaccine. In all instances,

live vaccines were superior to dead ones, and with at least one pair of nonpathogenic strains the nonmultiplying organisms were found to be superior to the multiplying ones, thus precluding the possibility that multiplication plays an important role. The *absolute* level of immunity is not only a function of the factors just mentioned, but likewise of the severity of the challenge dose.

Many workers emphasize that acquired antituberculous immunity is always of a relative nature and never able to confer to the vaccinated animal the power to completely destroy and eliminate all virulent tubercle bacilli with which it is infected. It is worth recalling several facts in this connection. As long as large infective doses are used, tuberculosis is a fatal disease for susceptible animals; but, as the infective dose is lowered, the survival times become longer, and, with small infective doses, it is possible to keep susceptible animals alive and in apparent good health for very long periods of time. In the present writers' experience, mice can survive for at least 550 days without showing signs of illness. When sacrificed at this point, they show the kind of gross lesions typical of chronic murine tuberculosis, and fully virulent tubercle bacilli can be recovered from their spleens and lungs. The same is true for guinea pigs. In a number of instances in which animals were infected with small numbers of tubercle bacilli (1–100 organisms), they developed a limited disease with local lymptoms, but failed consistently to die of generalized tuberculosis (27–29). Even with much larger infective doses a varying number of animals in a group often survive for a very long time and fail to die spontaneously within the observation period. Published protocols contain many such examples; some are found among the control animals in the present paper. The mice used in the present study were of a highly inbred strain. Therefore, it seems most likely that the long survivors owe their relative resistance to an immunity acquired with the infection and not to a different genetic susceptibility. Such mice did not overcome their infection by eliminating all invading bacteria from their organisms, but they reached a stage in which they lived in a state of equilibrium with them. The proportion of animals of a group who fail to die at the first impact of the infection increases with diminishing challenge doses. Huge infective doses similar to the ones used in most experimental work are rare under natural conditions. It may well be that the ability of humans to live with minimal or even more severe tuberculous infections without showing clinical signs of tuberculosis is due to mechanisms similar to the ones which prevail in these mice.

A paradoxical observation is illustrated in the curves of figure 4. At a certain point in the experiment, nonvaccinated mice had a better chance to survive than vaccinated groups whose survival curves showed a steady decline throughout the observation period. This phenomenon might reflect a difference between vaccinated and nonvaccinated animals in the initial distribution of virulent bacilli throughout the animal body as it occurs in the early phase of the infection. If this occurs, it would presumably be reflected in a different development of tuberculous lesions in various organs of these animals. The fact that vaccinated mice consistently showed much larger spleens than nonvaccinated animals who survived the challenge infection for the same length of time might indicate the presence of such a phenomenon.

The observation of animals surviving after infection with large numbers of virulent bacteria and continuing to harbor such bacilli in their organs in large numbers and in fully virulent state leads to the following working hypothesis:

> Acquired immunity in tuberculosis is based on the ability of the host to live in a state of equilibrium with the tubercle bacillus rather than on its power to eradicate the bacilli from its organism. Under natural conditions in man, this ability is often acquired during a minimal infection in which the host acquires the ability to check the infection at the same rate as the bacilli multiply. Under experimental conditions, it can be shown that virulent tubercle bacilli often survive in the animal for long periods of time without causing manifest disease. It is suggested that, during this phase in which the bacilli survive in a resting stage without increasing continuously in number, they produce those antigens which are concerned in causing this type of immunity. It is conceivable, but not postulated, that the resting stage is essential for the production of these antigens.

This hypothesis would explain why, in the present experiments, H37Ra, which survives in the mouse without increasing in numbers, was a better immunizing agent than the multiplying BCG. It would also explain why BCG, the multiplication of which was interfered with by isoniazid but which was not completely eradicated from the organism by the action of the drug, provided an immunity which was of approximately the same level as it was with freely multiplying BCG. It is likely that there are differences between various myocbacterial strains in their ability to survive intracellularly as well as in their rate of producing and releasing the hypothetical antigen.

SUMMARY

Results are presented of a comparative study of various antituberculous vaccines in mice. The length of time that animals survived after challenge infection served as a measure of immunity. The immunizing properties of viable and killed preparations, as well as of multiplying and nonmultiplying viable vaccines, were compared. In all instances, viable vaccines were superior to killed bacterial preparations. When various light intensities were used to inactivate a standard BCG vaccine partially or completely, the resulting immunity was in direct proportion to the number of viable cells which remained in the vaccine after irradiation. The proportion of killed bacteria present had no noticeable effect. BCG vaccines killed by heat or phenol were inferior to living bacterial suspensions of the same strength. A high dose of isoniazid given throughout the pre-challenge vaccination period did not significantly reduce the immunizing properties of BCG vaccine. This indicated that the bacterial multiplication of a vaccine is not a factor essential for the degree of immunity obtained. This point was further demonstrated by comparing BCG vaccines (multiplying) with vaccines prepared from a nonmultiplying avirulent variant of tubercle bacilli (H37Ra). In every dosage compared, the H37Ra vaccine was equal or superior to BCG.

The duration of the immunity produced in mice by a relatively high dose of BCG is limited. The highest level was reached between three weeks and three months after vaccination. Mice vaccinated six months prior to infection showed a

significant decrease in immunity. Nine months after vaccination, practically no immunity persisted.

SUMARIO

La Viabilidad y la Multiplicación de las Vacunas en la Inmunización contra la Tuberculosis

Preséntanse los resultados de un estudio comparado de varias vacunas antituberculosas en ratones. El tiempo que los animales sobrevivieron después de una infección provocadora sirvió de medida de la inmunidad. Comparáronse las propiedades inmunizantes de preparaciones viables y muertas, así como de vacunas viables ya multiplicantes o no. En todos los casos, las vacunas viables resultaron superiores a las preparaciones bacterianas muertas. Cuando se usaron varias intensidades luminosas para inactivar total o parcialmente una vacuna BCG corriente, la inmunidad resultante quedaba en proporción directa al número de células viables que restaban en la vacuna después de la irradiación. La proporción de bacterias muertas presentes no ejerció efecto apreciable. Las vacunas BCG matadas al calor o con fenol fueron inferiores a las suspensiones bacterianas vivas de la misma concentración. Una dosis alta de isoniacida administrada durante todo el período de vacunación antes de la provocación no rebajó mayor cosa las propiedades inmunizantes de la vacuna BCG, indicando así que la multiplicación bacteriana en la vacuna no es un factor indispensable para la intensidad de la inmunidad obtenida. Se demostró además este punto comparando vacunas BCG (multiplicantes) con vacunas preparadas de una variante avirulenta no multiplicante de bacilos tuberculosos (H37RA). A todas las dosis comparadas, la vacuna H37Ra resultó igual o superior a BCG. Es limitada la duración de la inmunidad producida en los ratones por una dosis relativamente alta de BCG. El valor más alto fué alcanzado entre tres semanas y tres meses después de la vacunación. Los ratones vacunados seis meses antes de la infección revelaron una disminución importante de la inmunidad. A los nueve meses de la vacunación, apenas restaba la menor inmunidad.

RESUME

Viabilité et multiplication des vaccins dans l'immunisation contre la tuberculose

Exposé des résultats de l'étude comparative, chez la souris, de divers vaccins antituberculeux. La durée de survie des animaux après l'inoculation expérimentale servait de mesure d'immunité. Les propriétés immunisantes des préparations viables ou tuées, de même que la multiplication ou la non multiplication des vaccins viables furent comparées. Dans tous les cas, les vaccins viables se sont montrés supérieurs aux préparations bactériennes tuées. L'emploi de diverses intensités lumineuses, pour inactiver complètement ou partiellement le BCG étalon, a procuré un degré d'immunité directement proportionnel au nombre de cellules viables survivant dans le vaccin après l'irradiation. La proportion des bacilles tués présents ne déterminait aucun effet appréciable. Les vaccins BCG tués par la chaleur ou le phénol étaient inférieurs aux suspensions bactériennes vivantes de même concentration. Une dose élevée d'isoniazide, administrée pendant toute la période précédant la vaccination expérimentale, ne réduisait pas de façon significative les propriétés d'immunisation du BCG, ce qui montrait que la mutiplication bactérienne dans le vaccin n'était pas un facteur essentiel à l'égard du degré d'immunité obtenu. Ce point a été encore démontré par la comparaison des vaccins BCG (multiplication) avec les vaccins préparés à partir d'un variant du bacille tuberculeux (H37Ra), avirulent et ne se multipliantpas. Pour toutes les doses, la comparaison a démontré que le vaccin H37Ra était égal ou supérieur au BCG. La durée de l'immunité produite chez la souris par une dose relativement élevée de BCG est limitée. Le maximum était atteint entre trois semaines et trois mois après la vaccination. Les souris vaccinées six mois avant l'infection présentaient une réduction appréciable de l'immunité. Neuf mois après la vaccination, il ne subsistait pratiquement aucune immunité.

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THE MAXIMAL DIFFUSING CAPACITY OF THELUNG IN CHRONIC OBSTRUCTIVE DISEASE OF THE AIRWAYS[1, 2, 3]

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INTRODUCTION

The need for means to detect and quantitate damage to the diffusing surface of the lungs in patients with chronic obstructive disease of the airways was recognized as early as 1915. At that time Marie Krogh (1) attempted to use measurements of the diffusing capacity of the lung[6] for this purpose, but her techniques were inadequate to assure valid results in patients with obstruction of the airways. In the years following 1946, this difficulty was largely overcome by methods developed by Lilienthal, Riley, and others (2–5). Using these methods, Donald, Renzetti, Riley, and Cournand (6) studied 14 patients with chronic obstructive disease of the airways and found that low values indicated damage to the pulmonary membrane. Interpretation of the data was difficult because the determination took into account only that portion of the diffusing surface participating in gas exchange at rest.

In order to obtain values related to the entire diffusing surface, studies during exercise were undertaken. It was found that with increasing exercise a maximal value for diffusing capacity was reached which could not be exceeded despite more strenuous exercise (7). This observation, corroborated by Filley and others (8), implied that, in contrast to the resting value, the maximal value for diffusing capacity was a function of the characteristics of the entire pulmonary membrane. Normal standards were then established for men of different sizes and ages (9), thus providing a basis for quantitation of the reduction of maximal diffusing capacity in patients with pulmonary disease.

The present study of the maximal diffusing capacity of the lungs in 27 patients

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[2] Presented in part before the Medical Session, as part of the session on *Nontuberculous Pulmonary Disease*, at the annual meeting of the National Tuberculosis Association, Atlantic City, New Jersey, on May 17, 1954.

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[6] The diffusing capacity of the lung may be defined as the quantity of reference gas (in practice, carbon monoxide or oxygen) crossing the pulmonary membrane per millimeter of mean pressure difference between alveolar gas and pulmonary capillary blood.

with chronic obstructive disease of the airways was undertaken to examine the relationship between the degree of obstruction of the airways and of damage to the diffusing surface of the lungs.

METHODS

Lung volumes and maximum breathing capacities were measured by methods described by Baldwin, Cournand, and Richards (10).

Expired gas and arterial blood were collected during exercise on a motor-driven treadmill after seven to ten minutes. Studies were performed by breathing gas mixtures of two different and carefully chosen concentrations of oxygen to allow calculation of venous admixture and diffusing capacity. Previous publications contain detailed descriptions of the technical and theoretical aspects of the methods (2–7) and of expected values of maximal diffusing capacity in normal subjects of different size and age (9).

SUBJECTS

Subjects were selected to provide a group of patients with chronic obstructive airway disease of mild to moderate degree with a minimum of other pulmonary

TABLE 1

PHYSICAL CHARACTERISTICS AND SYMPTOMATOLOGY OF 27 PATIENTS WITH CHRONIC OBSTRUCTIVE AIRWAY DISEASE

Subject	Sex	Age	Height	Duration of Dyspnea	History of Cough and Sputum	Pulmonary Artery Enlargement	History of Heart Failure
		years	*cm.*	*years*			
W. B.	M	58	165	20	Yes	Yes	Yes
E. Be.	M	62	160	4	Yes	No	No
G. B.	M	44	174	2	Yes	Yes	No
H. B.	M	53	182	4	Yes	No	No
E. Bu.	M	48	189	6	Yes	No	No
L. C.	M	51	173	4	Yes	No	No
St. F.	M	54	178	1	Yes	No	No
D. G.	M	50	182	6	No	No	No
F. H.	M	65	180	4	Yes	No	No
W. H.	M	58	168	6	Yes	No	No
E. H.	M	42	168	13	Yes	Yes	Yes
N. J.	F	33	160	10	Yes	Yes	No
H. K.	M	42	168	3	Yes	No	No
E. K.	M	47	175	6	Yes	No	No
H. L.	M	53	161	3	Yes	No	No
W. M.	M	53	185	2	Yes	No	No
L. M.	M	56	168	2	Yes	No	No
J. M.	M	42	173	20	Yes	Yes	Yes
F. M.	M	39	163	4	Yes	Yes	Yes
P. P.	M	70	168	11	Yes	No	No
C. R.	M	53	172	10	Yes	No	No
W. C. S.	M	65	175	20	Yes	No	No
W. B. S.	M	49	187	3	Yes	No	No
F. S.	M	46	173	15	Yes	Yes	No
C. T.	M	62	174	3	No	No	No
P. W.	M	70	173	5	Yes	Yes	No
B. W.	M	52	172	3	Yes	Yes	No

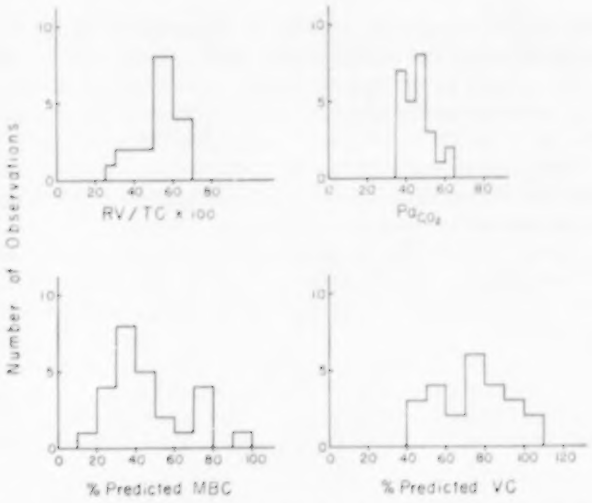

FIG. 1. Frequency distributions of residual volume-total capacity ratio (RV/TC), arterial carbon dioxide tension in millimeters of mercury ($P_{a_{CO_2}}$), maximum breathing capacity (MBC), and vital capacity (VC).

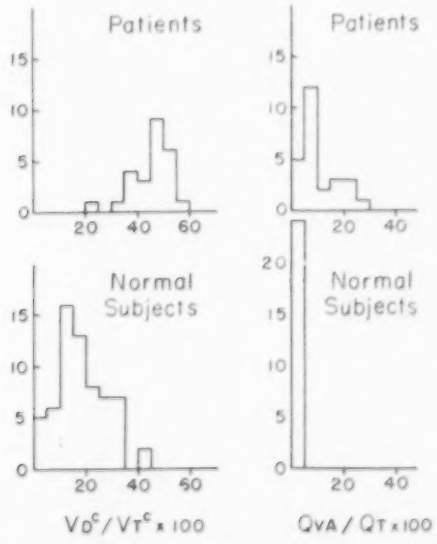

FIG. 2. Frequency distributions of the ratio between dead space and tidal volume (V_D^c/V_T^c) and the ratio between venous admixture and total blood flow (Q_{va}/Q_t). Number of cases is shown along the ordinate in each case. Since these measurements were made during exercise, studies of a comparable group of normal subjects are shown for comparison.

complications. Patients were not included in the study if any of the following conditions was present: asthmatic attacks within the past five years, large or multiple bullae, known bronchiectasis, or roentgenographic evidence of fibrosis, pneumoconiosis, or pneumonic infiltration. The necessity to perform moderate exercise eliminated patients who were completely incapacitated. The group, therefore, differed from many previously reported in that only patients with mild to moderate degrees of incapacity from apparently uncomplicated diffuse obstructive disease were included.

Upon completion of history, physical examination, roentgenography, fluoroscopy, and spirography, one female and 26 male patients satisfied the above criteria. The data relating to physical characteristics and symptomatology are presented in table 1.

TABLE 2

STUDIES ON LUNG VOLUME, VENTILATORY CAPACITY, AND DISTRIBUTION OF VENTILATION-PERFUSION RATIOS IN THE LUNGS OF 27 PATIENTS WITH CHRONIC OBSTRUCTIVE AIRWAY DISEASE

Subject	Vital Capacity		RV TC	Maximum Breathing Capacity		P_{ACO_2}*	P_{aO_2}*	$\frac{V_D}{V_T}$**	$\frac{Q_{VA}}{Q_T}$*	Response to Bronchodilator
	liter	*per cent predicted*	*per cent*	*l./min.*	*per cent predicted*	*mm. Hg*		*per cent*	*per cent*	
W. B.	2.13	64	55	59	66	54	78	51	6	Slight
E. Be.	2.09	61	—	27	31	38	90	49	4	Slight
G. B.	2.01	51	64	35	32	46	78	48	4	Moderate
H. B.	3.59	93	40	107	91	44	84	38	5	Moderate
E. Bu.	3.56	89	53	45	41	39	61	45	12	Moderate
L. C.	3.10	83	66	38	37	48	87	48	3	Moderate
St. F.	2.84	73	44	80	77	38	80	22	9	Marked
D. G.	2.04	49	63	28	15	47	48	51	21	Moderate
F. H.	3.84	127	54	68	75	45	84	51	5	Slight
W. H.	1.78	52	—	38	41	46	83	51	4	Slight
E. H.	3.48	97	—	34	34	60†	89†	41†	6†	Marked
N. J.	1.74	60	—	35	38	43	72	41	12	Moderate
H. K.	3.15	89	57	71	74	42	85	47	5	None
E. K.	3.50	90	31	36	34	36	68	56	15	Marked
H. L.	1.80	54	—	22	24	52	57	45	18	Moderate
W. M.	2.52	54	57	41	24	46	86	51	4	Moderate
L. M.	2.60	74	—	39	42	40	87	36	5	Moderate
J. M.	2.95	76	—	34	30	59	49	48	18	Slight
F. M.	2.66	73	51	26	25	53	53	52	7	Slight
P. P.	2.83	85	—	40	47	58	88	35	5	Moderate
C. R.	2.69	72	51	35	35	44	91	37	5	Marked
W. C. S.	1.53	44	59	32	36	42	76	42	7	Moderate
W. B. S.	5.98	146	23	86	75	39	63	33	16	Slight
F. S.	3.47	91	—	45	46	45	77	49	8	Moderate
C. T.	2.81	78	—	38	41	40	80	46	7	Slight
P. W.	3.65	106	38	51	58	36	73	39	10	Slight
B. W.	2.55	69	—	45	45	42	59	49	20	Moderate

* Measured during treadmill exercise breathing air.

† Measured during treadmill exercise breathing 24 per cent oxygen.

The severity of symptoms ranged from mild, with dyspnea only during fairly heavy exercise or in the presence of acute respiratory infection (W.B.S. and H.B.), to severe, with marked dyspnea on climbing stairs (E.H. and F.M.). Within 18 months of study, both of the patients in the latter category succumbed in acute respiratory acidosis outside the hospital.

At the time of study all patients had shown unremitting ventilatory disability over a long period of time. Only one patient (J.M., 42 years of age) gave a history of asthmatic attacks. These attacks occurred between seven and thirteen years of age and between twenty-three and twenty-six without further difficulty until approximately thirty-five years of age, when repeated respiratory infections developed with subsequent progressive exertional dyspnea and, at forty, symptoms of right heart failure.

Although they were never free of symptoms, patients W.C.S. and C.T. noted marked increase in dyspnea during periods of emotional stress.

TABLE 3

VALUES FOR OBSERVED AND PREDICTED MAXIMAL DIFFUSING CAPACITY, OXYGEN CONSUMPTION, RESPIRATORY EXCHANGE RATIO, AND TREADMILL GRADE AND SPEED FOR 27 PATIENTS WITH CHRONIC OBSTRUCTIVE AIRWAY DISEASE

Subject	Maximal Diffusing Capacity		Oxygen Consumption	R	Treadmill	
	Observed	Predicted			Grade	Speed
			cc./min.		*degrees*	*m.p.h.*
W. B.	18	37	406	1.05	Level	0.6
E. Be.	14	37	387	1.05	Level	0.8
G. B.	19	51	602	1.05	4.0	1.2
H. B.	45	51	1,130	0.89	4.0	2.3
E. Bu.	17	58	890	0.97	4.6	0.9
L. C.	22	46	624	0.96	Level	1.1
St. F.	43	48	1,000	0.97	5.3	1.3
D. G.	13	53	530	0.86	Level	0.7
F. H.	29	43	678	0.88	Level	1.5
W. H.	19	39	539	0.86	Level	1.5
E. H.	23	48	860	0.91	2.8	1.8
N. J.	13	45	488	1.07	Level	2.0
H. K.	24	42	612	0.96	Level	1.5
E. K.	21	50	720	0.83	Level	1.6
H. L.	22	37	693	1.01	Level	1.3
W. M.	34	53	615	0.95	Level	1.2
L. M.	35	40	650	0.95	3.8	2.0
J. M.	20	51	805	0.90	Level	1.9
F. M.	11	46	584	0.91	Level	0.8
P. P.	17	32	563	1.13	Level	1.0
C. R.	38	44	760	1.13	3.8	1.8
W. C. S.	31	40	554	0.84	Level	1.1
W. B. S.	19	56	2,098	1.01	6.1	2.0
F. S.	25	49	681	0.92	1.4	2.4
C. T.	31	41	616	0.87	Level	0.7
P. W.	21	36	782	0.88	Level	3.1
B. W.	18	44	683	0.92	Level	1.5

In the remaining patients, ventilatory disability was less variable except in association with respiratory infection.

As shown in table 1, 4 patients gave a history of right ventricular failure. Six other patients had prominence of the pulmonary artery on fluoroscopy, and 3 of these had changes in the electrocardiogram compatible with right ventricular strain.

In varying degrees, all patients showed increase in antero-posterior diameter of the chest, low diaphragms, limitation of diaphragmatic motion, and expiratory obstruction on physical examination and fluoroscopy.

The characteristics of the patients were further defined by studies of lung volume, ventilatory capacity, and the distribution of ventilation-perfusion ratios in the lungs. The results of these studies are given in table 2 and in figures 1 and 2. It may be seen in figure 1 that in most instances there was significant elevation of the ratio of residual volume to total capacity and that several patients showed elevation of arterial carbon dioxide tension. In almost all cases, the maximum breathing capacity and vital capacity were considerably reduced. Although not shown in figure 1, the shape of the vital capacity tracing was characteristic of expiratory obstruction in all cases. With a single exception

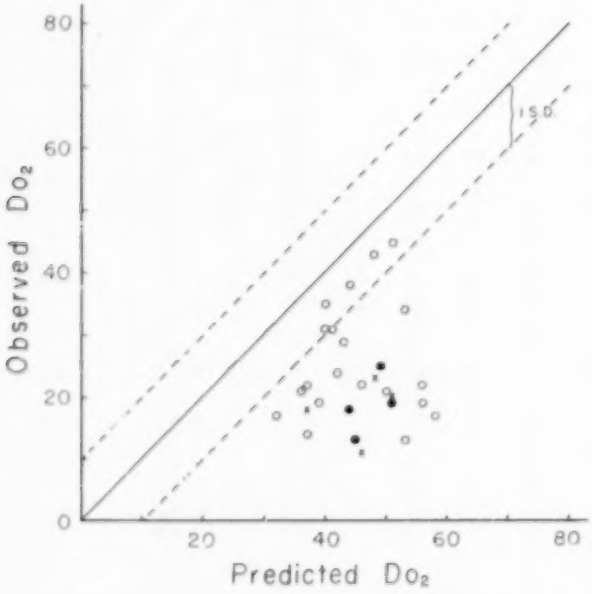

FIG. 3. Comparison of observed and predicted maximal diffusing capacity. Open circles represent patients without evidence of cardiac involvement. Solid dots represent patients with enlargement of the pulmonary artery on roentgenogram or electrocardiographic changes compatible with right ventricular strain. Crosses represent patients with a history of cardiac failure.

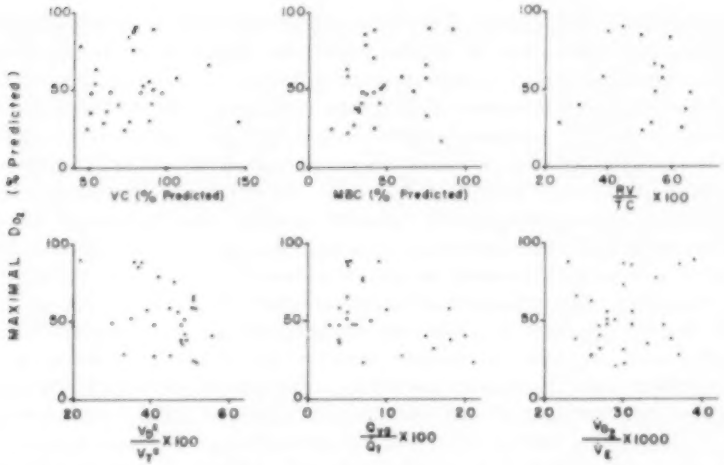

FIG. 4. Scatter-diagrams showing the relationship of the maximal diffusing capacity to vital capacity, maximum breathing capacity, residual volume-total capacity ratio, dead space-tidal volume ratio, venous admixture-total blood flow ratio, and the ratio between oxygen uptake and minute volume of ventilation ($\dot{V}_{O_2}/\dot{V}_E$).

(H.K.), all patients showed at least slight improvement after inhalation of a nebulized bronchodilator (epinephrine, Isuprel ®, or Vaponefrin ®) (table 2).

In figure 2, the ratios of dead space to tidal volume and of venous admixture to total flow are shown to be increased in most of the patients, indicating extensive variation in ventilation-perfusion ratio in different parts of the lung.

RESULTS[7]

Values for observed and predicted maximal diffusing capacity, oxygen consumption, respiratory exchange ratio, and treadmill grade and speed are given in table 3. In figure 3, observed and predicted values for maximal diffusing capacity for each subject are compared. Six subjects had normal diffusing capacities. The remainder of the subjects had low diffusing capacities. Patients with cardiac involvement all had low diffusing capacities.

In figure 4 the diffusing capacity is compared with the vital capacity, maximum breathing capacity, residual volume-total capacity ratio, dead space-tidal volume ratio, venous admixture-total blood flow ratio, and rate of oxygen removal (ratio between oxygen consumption and ventilation) (10). The correlation between these measurements and the maximal diffusing capacity is poor.

DISCUSSION

The upper three scatter-diagrams in figure 4 serve as a point of departure for discussion of the relationships between airway obstruction and damage to the

[7] A table of raw data from all studies has been deposited with the American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C.

diffusing surface of the lungs. The findings plotted along the abscissae provide an estimate of the degree of airway obstruction; and the maximal diffusing capacity, plotted along the ordinates, provides an estimate of the extent of damage to the diffusing surface of the lungs. Justification for the use of the vital capacity, maximum breathing capacity, and residual volume-total capacity ratio is scarcely needed. A great many studies have demonstrated that obstructive disease is accompanied by reduction in the maximum breathing capacity and, when severe, by reduction in the vital capacity and elevation of the ratio between residual volume and total capacity. The use of the maximal diffusing capacity in evaluating damage to the structures of the alveolar walls has no such well-established precedent. This measurement has been shown to be reduced in some diseases in which the diffusing surface is damaged, but both technical and physiological factors entering into the interpretation require further discussion. This is particularly true because of the complexities introduced by the presence of airway obstruction and limitation of exercise tolerance.

Technical factors leading to error in the estimation of diffusing capacity have been discussed in detail in a previous paper (7). In general, errors are smallest when the arterial oxygen tension during low oxygen breathing is less than 50 mm. of mercury and when the mean gradient of oxygen tension between alveolar gas and pulmonary capillary blood is large. The arterial oxygen tension may be controlled by altering the concentration of oxygen in the inspired air. The mean gradient is a function of the diffusing capacity and the rate of oxygen consumption and may therefore be controlled to some extent by altering the grade of exercise. In these studies the arterial oxygen tension was kept under 50 mm. of mercury and the mean gradient ranged between 20 and 53 mm. of mercury. Therefore, a high degree of confidence in the technical reliability of the determinations is justified.

The diffusing capacity increases in response to increase in the number of pulmonary capillaries perfused. No circumstances are known in which the maximal diffusing capacity is increased by pathologic changes in the diffusing surface of the lungs. It is almost certain, therefore, that the 6 patients with normal diffusing capacities had no significant damage to the diffusing surface of their lungs.

Decrease in the diffusing capacity may result from reduction of the area of the pulmonary membrane or reduction in its permeability for oxygen per unit area. Disease processes may produce either or both of these effects, the former by destruction of pulmonary capillaries and the latter by changing the physico-chemical properties or increasing the thickness of the pulmonary membrane. A low diffusing capacity may also result if exercise is not sufficiently strenuous to achieve a maximal value (7) or if some alveoli are completely nonventilated because of bronchial obstruction. In either of these cases, the determined diffusing capacity would not reflect the character of the entire diffusing surface of the lungs. It is of interest to consider which of these mechanisms might be responsible for the low maximal diffusing capacities found in 21 of the patients.

Despite their limited exercise tolerance, 16 patients with low diffusing capaci-

ties achieved levels of exercise which gave maximal values in normal subjects of comparable age. One of these subjects (W.B.S.) achieved a level of exercise far in excess of that necessary to produce maximal values in young normal subjects. In these subjects, it is reasonable to assume that the reduced diffusing capacity was not owing to incomplete perfusion of the pulmonary capillary bed. In the remaining 5 patients, the level of exercise was so low that this assumption is not warranted.

In the 16 patients who exercised adequately, the possible role of total obstruction of some airways is more difficult to assess. Although nebulized bronchodilator was usually administered immediately prior to study to minimize airway obstruction, the possibility that totally obstructed areas did account in part for the low diffusing capacity cannot be excluded in all cases.

There were 5 patients in whom the functional characteristics were relatively clear cut and in whom interpretations could therefore be made with greatest confidence. One patient (W.B.S.) had mild airway obstruction and marked reduction in diffusing capacity and 4 (L.M., C.R., W.C.S., C.T.) had severe airway obstruction and normal diffusing capacities. The first patient almost certainly had extensive damage to the diffusing surface of his lungs with only mild obstructive manifestations, while in the latter group the diffusing surface was presumably intact in spite of severe airway obstruction. These findings, standing at either end of the wide range shown in figure 4, provide strong evidence that there need be no correlation between the degree of airway obstruction and the maximal diffusing capacity.

The poor correlation between the capacities for ventilation and diffusion in chronic obstructive disease of the airways may parallel the poor correlation between evaluations based on clinical and on pathological evidence. The clinician's estimate of severity is usually based on such findings as exertional dyspnea, wheezing, thoracic deformity, low, flat diaphragms, diminution of breath sounds, hyper-resonance, and roentgenographic evidence of hyperinflation. These findings may be bolstered by such laboratory evidence as a high residual volume, a low maximum breathing capacity, or slowed expiration as visualized in the spirogram. Without exception, such clinical and laboratory findings can be accounted for by airway obstruction without necessarily implicating damage to the alveolar walls. The pathologist's estimate of severity, on the other hand, depends upon the extent of damage to the alveolar walls as well as the state of the airways. As, according to the findings in the present study, obstruction of airways and impairment of diffusion need not parallel one another, it is understandable that the clinician and the pathologist, looking at different aspects of the disease, might disagree (11, 12).

The correlation between reduction in the maximal diffusing capacity and anatomic changes in the various structures of the alveolar walls has not yet been studied. Nevertheless, it seems relatively certain that destruction of alveolar walls is accompanied by reduction in the diffusing capacity. The converse may not be true, however, for changes in the number of pulmonary capillaries or in the physico-chemical characteristics of the diffusing surface, which would lower

the diffusing capacity, might occur without complete disintegration of the alveolar wall. Further study of the relationship between structure and function in the lung is necessary if physiological findings are to be used to draw inferences regarding structure or if pathological findings are to be used to draw inferences regarding function. Both approaches are desirable, but the physiological approach must be relied upon for most of our knowledge of the evolution of changes occurring during the course of the disease.

Determination of the maximal diffusing capacity makes possible a description of sequential changes in a function of the lung which has not previously been adequately studied. To this extent it should help in understanding the natural history of the various types of chronic obstructive disease of the airways.

SUMMARY

The maximal diffusing capacity was measured in 27 subjects with chronic obstructive disease of the airways. Normal maximal diffusing capacity was found in 6 subjects, low values were found in the remaining 21 subjects.

Correlation between the maximal diffusing capacity and lung volumes and ventilatory capacity was poor, suggesting that there need be no correlation between the degree of airway obstruction and severity of damage to the diffusing surface of the lung.

This poor correlation may explain in part the discrepancies between estimates of severity of involvement by the clinicians, whose evaluation lays primary stress on the degree of airway obstruction, and the pathologist, whose evaluation lays primary stress on the extent of disintegration of the walls of the alveoli.

SUMARIO

La Máxima Capacidad Difusora del Pulmón en la Enfermedad Oclusiva Crónica de las Vías Aéreas

En 27 sujetos que tenían afección oclusiva crónica de las vías aéreas se midió la capacidad difusora máxima. En 6, se encontró capacidad difusora máxima normal; en los 21 restantes, se descubrieron valores bajos.

La correlación entre la capacidad difusora máxima y los volúmenes pulmonares y la capacidad ventiladora fué mala, indicando que no se necesita correlación entre la magnitud de la oclusión de las vías aéreas y la gravedad de la lesión con la superficie difusora del pulmón.

Esa mala correlación puede explicar en parte las discrepancias entre los cómputos de la gravedad de la lesión por los clínicos, cuya valuación hace primordialmente hincapié en el grado de la obstrucción de las vías aéreas, y el patólogo, cuya valuación hace primordialmente hincapié en la extensión de la desintegración de las paredes de los alvéolos.

RESUME

La capacité de diffusion maxima du poumon dans l'obstruction chronique des voies respiratoires

La capacité de diffusion maxima a été déterminée chez 27 sujets affectés d'obstruction chronique des voies respiratoires. La capacité de diffusion maxima normale a été observée chez 6 sujets; des valeurs inférieures ont été observées chez les 21 autres.

La corrélation entre la capacité de diffusion maxima et les volumes pulmonaires et la capacité de ventilation était insuffisante, ce qui permettait de supposer l'absence de cor-

rélation entre le degré d'obstruction de la voie respiratoire et la valeur de l'altération de la surface de diffusion du poumon.

Cette corrélation inadéquate peut expliquer partiellement les écarts observés dans l'évaluation de la gravité de l'obstruction par le clinicien, dont l'evaluation qui repose surtout sur le degré de l'obstruction de la voie respiratoire, et par l'histologiste, évaluation repose surtout sur l'importance de l'altération des parois alvéolaires.

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STUDIES ON THE METABOLISM OF THE ACID-FAST BACTERIA[1]

I. Indications of Intermediate Pathways of Glucose Dissimilation by *Mycobacterium* 607

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INTRODUCTION

All members of the genus *Mycobacterium* which have been studied by various investigators appear to be obligate aerobes (1). In general, the relatively rapid-growing species oxidize a much wider range of substrates than the slow-growing species and, with the exception of carbon dioxide and a trace of acid, end products of carbohydrate metabolism have not been detected (2, 3, 4). The rates of oxidation of utilizable compounds are also much greater in the rapidly growing members of the genus. For this reason, the intermediary metabolism of the saprophytic species has been more fully studied than the slow-growing strains of tubercle bacilli.

In studying the oxidation of glucose by *Mycobacterium phlei*, Edson and Hunter (5) found that approximately one-third of the metabolized glucose was converted to carbon dioxide and water, and approximately two-thirds of the substrate was assimilated by the bacteria. Arsenite interfered with glucose metabolism, causing the accumulation of small amounts of pyruvate.

Geronimus (6) observed that clarified extracts of *Mycobacterium smegmatis* took up oxygen in the presence of hexosediphosphate and methylene blue. Faine, Whiteside, and Edson (7) obtained similar results with *Mycobacterium phlei* and *Mycobacterium smegmatis*. Although the oxygen uptake of intact cells was not stimulated greatly by hexosephosphates, there was a rapid reduction of methylene blue when either glucose-1-phosphate or fructose-1,6-diphosphate was added to cell-free extracts under anaerobic conditions. In the absence of methylene blue, fructose-1,6-diphosphate but not glucose-1-phosphate was converted to triosephosphate. Under anaerobic conditions, methylene blue was reduced by hexosephosphates without the intermediary formation of triosephosphate.

In the present study, it was found that gluconic acid was oxidized by *Mycobacterium* 607, and the possibility that glucose was oxidized directly (hexosemonophosphate shunt) via a pathway similar to that of Dickens (8) was investigated. To test this possibility, the oxidation of the following compounds was studied: gluconate, 6-phosphogluconate, D-ribose and D-xylose. By applying the principle of simultaneous adaptation (9), the results of this investigation suggest that, while many of the reactions of the hexosemonophosphate shunt are operative in

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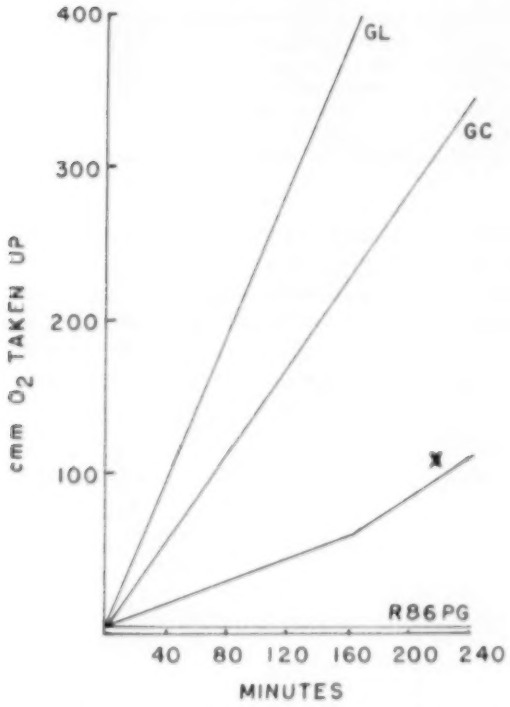

FIG. 1. Oxidation of glucose, gluconate, 6-phosphogluconate, D-ribose, and D-xylose by glucose-grown cells of *Mycobacterium* 607. Total volume 3.2 ml., containing 1.0 ml. of cell suspension, 1.0 ml. of M/15 phosphate buffer, pH 7.0, 0.2 ml. of 10 per cent potassium hydroxide in the center well, 0.2 ml. of 0.05 M substrate or distilled water in the side arm, and distilled water to desired volume. Endogenous respiration subtracted from all curves.
GL: glucose; *GC:* gluconate; *X:* D-xylose; *R:* D-ribose; *6PG:* 6-phosphogluconate.

Mycobacterium 607, glucose-grown cells do not utilize this mechanism as the main pathway of glucose oxidation.

EXPERIMENTAL METHODS

The bacterium employed in this study was the relatively fast-growing, avirulent *Mycobacterium*, ATCC strain 607.[2] The cells were grown in liter Roux bottles on the synthetic medium of Proskauer and Beck (10), modified to contain either glucose or calcium gluconate in 2 per cent concentration as the carbon source. After forty-eight hours' incubation at 37°C., the cells were harvested and introduced into a 500 ml. Erlenmeyer flask containing a 2 to 4 cm. layer of glass beads. The flask was rotated for approximately five minutes until a homogeneous suspension of bacilli resulted. The cells were then suspended in distilled water, centrifuged, resuspended in M/15 phosphate buffer, pH 7.0, and aerated on a mechanical shaking machine for forty-eight hours in order to reduce the high rate of en-

[2] This species is said to be Koch's original strain of tubercle bacillus; however it grows rapidly on nutrient agar and is avirulent.

dogenous respiration. Cells were then rewashed three times in distilled water, suspended in distilled water, and stored at approximately 4°C. until needed.

Oxygen consumption was determined by the "direct method" of Warburg (11). The bath temperature was 37.2°C. Substrates were dissolved in distilled water, and the pH was adjusted to 7.0 with HCl or NaOH. Veronal buffer was prepared by the method of Michaelis (12). The barium salt of 6-phosphogluconate was prepared from glucose-6-phosphate (barium salt) by bromine oxidation, as described by Seegmiller and Horecker (13).

RESULTS

As illustrated in figure 1, with the glucose-grown cells of *Mycobacterium* 607, glucose was immediately oxidized, and there was a lag period of approximately twenty minutes before gluconate was metabolized. A considerable period of time also elapsed before D-xylose was oxidized at the maximum rate, and D-ribose and 6-phosphogluconate did not appear to stimulate the rate of oxygen uptake. When this microorganism was grown on the gluconate medium, all of the substrates were immediately oxidized (figure 2). It should be pointed out that figures 1 and 2 are comparable in every respect, i.e., cells were grown, washed, and

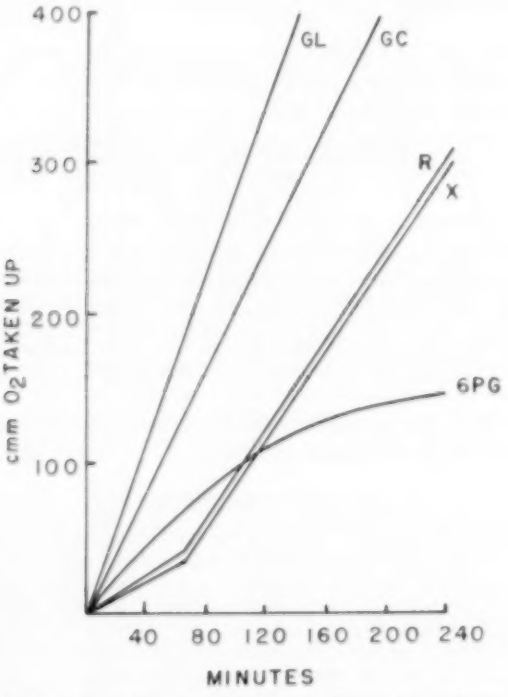

FIG. 2. Oxidation of glucose, gluconate, 6-phosphogluconate, D-ribose, and D-xylose by gluconate-grown cells of *Mycobacterium* 607. Endogenous respiration subtracted from all curves. Flask contents and legend same as figure 1.

TABLE 1

EFFECT OF PHOSPHATE ON THE RATES OF OXIDATION OF SOME HEXOSEPHOSPHATES BY RESTING CELLS OF GLUCOSE-GROWN MYCOBACTERIUM 607

	Cu. Mm. of Oxygen per 120 Min.	
	Phosphate Buffer	Veronal Buffer
Glucose	180	224
Glucose-6-phosphate	3	41
Fructose-1,6-diphosphate	5	60

Total volume 3.2 ml., containing 1.0 ml. of cell suspension, 1.0 ml. of either M/15 phosphate buffer or M/10 veronal buffer, 0.2 ml. of 10 per cent potassium hydroxide in the center walls, 0.2 ml. of 0.05M substrates or distilled water in the side-arm and distilled water to desired volume. Endogenous respiration has been subtracted from all of the figures.

aerated at the same time. These results suggest that, while the hexosemonophosphate shunt would appear to be a possible pathway of glucose oxidation, it is not the main route by which glucose-grown cells of *Mycobacterium* 607 dissimilate this compound.

The influence of inorganic phosphate on the rates of oxidation of glucose-6-phosphate and fructose-1,6-diphosphate is presented in table 1. Glucose-grown cells of *Mycobacterium* 607 were washed five times in demineralized water by centrifugation, and the rates of oxidation of these compounds in phosphate and veronal buffers were compared.

DISCUSSION

Although it is thought that glucose is frequently dissimilated aerobically via the Embden-Meyerhof scheme (14), there is evidence to suggest that alternate pathways are also possible. Campbell and Norris (15) have obtained evidence that glucose is oxidized to gluconic and 2-ketogluconic acids by *Pseudomonas aeruginosa*. Dickens and Glock (16) have suggested that hexosephosphate may be converted to ribose phosphate in yeast. Cohen and Scott (17) have made similar observations.

In the present investigation, the increase in the rates of oxidation of 6-phosphogluconate and D-ribose by gluconate-grown cells of *Mycobacterium* 607 was very marked, and this suggests that the direct oxidative pathway may be an alternate mechanism for the oxidation of glucose in this organism. While 2-ketogluconate was oxidized by *Mycobacterium* 607, the rates of oxidation by glucose and gluconate-grown cells were approximately the same.

It is interesting to note that Youmans and Youmans (18) have found that gluconic acid stimulates the growth of the H37Rv strain of tubercle bacillus to approximately the same degree as glucose.

It has been suggested that the slow rate of oxidation of hexosephosphates by some of the acid-fast bacteria may be the result of impermeability of the cells to these substrates (19). Wood and Schwerdt (20) have found that phosphate

inhibits the oxidation of these compounds by *Pseudomonas fluorescens*. While the impermeability of the cells of the mycobacteria to the hexosephosphates may still be of importance in determining the rates of oxidation of these compounds, it appears that inorganic phosphate in some way also interferes with these reactions. The oxidation of glucose-6-phosphate and fructose-1,6-diphosphate was apparent when the reactions were determined in veronal buffer and was not adaptive in nature.

SUMMARY

Simultaneous adaptation experiments suggest that the direct oxidation of glucose via the hexosemonophosphate shunt is probably not the main pathway of glucose dissimilation by glucose-grown cells of *Mycobacterium* 607.

While very little oxygen uptake was observed in the presence of the hexosephosphates, it has been found in this investigation that the presence of inorganic phosphate may inhibit the oxidation of these intermediates in some way. When veronal buffer was substituted for phosphate buffer, the rates of oxidation of glucose-6-phosphate and fructose-1,6-diphosphate were increased. Thus, the degradation of glucose via the Embden-Meyerhof scheme in the acid-fast bacteria is further substantiated.

SUMARIO

Estudios del Metabolismo de las Bacterias Acidorresistentes: I. Indicaciones de Vías Intermedias de de Desasimilación de la Glucosa por el Mycobacterium 607

Experimentos simultáneos de adaptación sugieren que la oxidación directa de la glucosa por la vía de la desviación hexosemonofosfática no es probablemente la principal vía de la desasimilación de la glucosa por las células del *Mycobacterium* 607 cultivadas en glucosa.

Aunque se observó muy poca absorción de oxígeno en presencia de los hexomonofosfatos, descubrióse en esta investigación que la presencia de fosfato inorgánico puede inhibir en alguna forma la oxidación de dichos intermediarios. Cuando se utilizó como amortiguador veronal en vez de fosfato, se elevaron los índices de oxidación de glucosa-6-fosfato y de fructosa-1,6-bifosfato. Queda, pues, de nuevo comprobada la degradación de la glucosa por vía del esquema de Embden-Meyerhof en las bacterias ácidorresistentes.

RESUME

Etude sur le métabolisme des bactéries acido-résistantes: I. Les signes de voies intermédiaires de dissimilation du glucose par le Mycobacterium 607

Des expériences d'adaptation simultanées suggèrent que l'oxydation directe du glucose par le shunt fructose-6-phosphate n'est probablement pas la voie principale de dissimilation du glucose par les cellules du *Mycobacterium* 607 cultivées dans le glucose.

Tandis qu'une très faible absorption se manifestait en présence de fructose-6-phosphate, il a été découvert, au cours de cette étude, que la présence de phosphate inorganique pouvait inhiber d'une certaine manière l'oxydation de ces intermédiaires. Quand un tampon véronal était substitué au tampon phosphate, les taux d'oxydation du fructose 1,6-diphosphate étaient augmentés. Ainsi, la dégradation du glucose par le procédé Embden-Meyerhof dans les bactéries acido-résistantes reçoit une nouvelle confirmation.

Acknowledgment

The writers wish to thank Dr. Emil Bogen of Olive View Sanatorium, Olive View, California, for his encouragement and advice with respect to numerous aspects of this work.

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STUDIES ON THE METABOLISM OF THE ACID-FAST BACTERIA[1]

II. Indications of Intermediate Pathways of Acetate Oxidation

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(Received for publication August 2, 1954)

INTRODUCTION

Numerous species of acid-fast bacteria are able to oxidize many of the intermediate compounds of the Krebs tricarboxylic acid cycle (1, 2, 3). Previous investigations (4, 5) have shown that, in *Mycobacterium phlei*, pyruvic acid is oxidized to carbon dioxide and water with acetic acid as an intermediate compound. Little is known of the pathway(s) of acetate oxidation of this group of microorganisms.

While washed suspensions of mycobacteria either do not oxidize citrate or oxidize this compound very slowly (6), Blakley (7) has demonstrated the enzymatic formation of citrate in *M. phlei* and suggests the functioning of a tricarboxylic acid cycle.

The technique of simultaneous adaptation (8) has been employed in the study of terminal respiration of numerous bacteria. The results in most cases have led the investigator to favor either the participation of a tricarboxylic acid cycle or a Thunberg-Knoop cycle for the oxidation of acetate.

In the present study, this technique is utilized to investigate the pathway of acetate oxidation in three members of the genus *Mycobacterium*.

EXPERIMENTAL METHODS

The acid-fast bacteria employed were the avirulent *Mycobacterium* ATCC, strain 607[3]; *Mycobacterium ranae*[3], streptomycin-susceptible (SMS); and *Mycobacterium ranae*, streptomycin-dependent (SMD). The streptomycin-dependent strain was originally obtained from the parent strain by Yegian and Budd (9). The cells were grown on the synthetic medium of Proskauer and Beck (10), from which the citrate and glycerol had been eliminated, and the various carbon sources were used in 2 per cent concentration.

The cells were harvested and aerated as previously described (11). Dried-cell preparations were obtained by desiccation over P_2O_5 as described by Stokes and Campbell (12). This technique has been employed by numerous investigators in order to overcome the impermeability of cells.

Oxygen consumption was measured by the standard Warburg method (13).

RESULTS

The relative rates of oxidation of some of the tricarboxylic cycle intermediates by glucose-grown cells of *Mycobacterium* 607 and *M. ranae* (SMS) are represented in figure 1. The cells of glucose-grown *M. ranae* (SMD) presented a pattern of

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oxidation of these compounds that was very similar to the pattern for *Mycobacterium* 607. In contrast to the parent strain, the relatively rapid rate of acetate oxidation was much reduced in the streptomycin-dependent strain of *M. ranae*, and there was little or no oxidation of citrate.

When acetate and citrate-grown cells were employed, there was no appreciable increase in the rates of oxidation of the intermediate compounds by *M. ranae* (SMS), which would seem to suggest that the pathway of terminal respiration of this strain is via a tricarboxylic acid cycle. On the other hand, there was an increase in the rates of oxidation of the dicarboxylic acids but not citric or the C_5 acid when acetate-grown cells of *Mycobacterium* 607 or *M. ranae* (SMD) were used (figure 2).

The effect of drying of the cells of *Mycobacterium* 607 and *M. ranae* (SMS) on the rates of oxidation of a number of the substrates is illustrated in figure 3. The relative rates of oxidation of most of the compounds were not changed; however, it was found that the rate of citrate oxidation was increased in *M. ranae* (SMS). This increase was not apparent when *Mycobacterium* 607 was used,

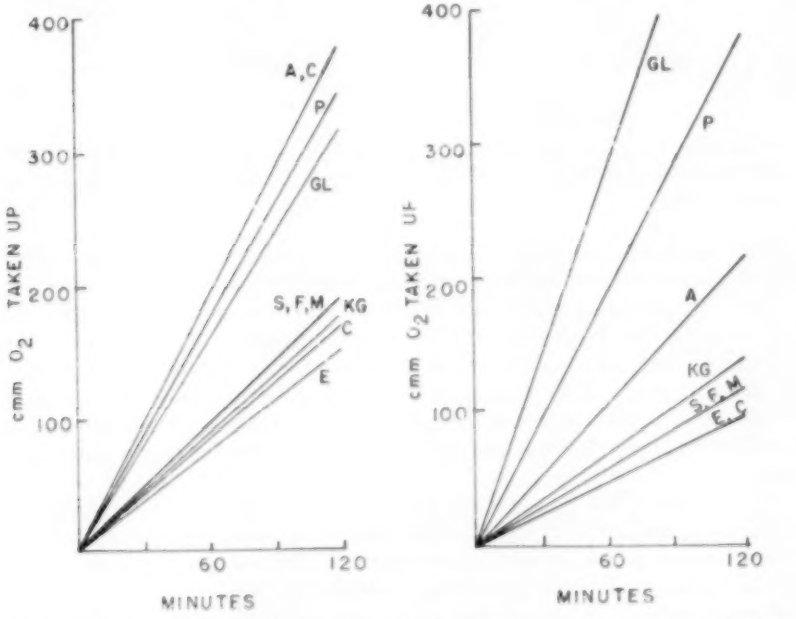

FIG. 1. Oxidation of various intermediates by glucose-grown cells of *M. ranae* (SMS) and *Mycobacterium* 607, left and right figures, respectively. Total volume 3.2 ml., containing 1.0 ml. of cell suspension, 1.0 ml. of M/15 phosphate buffer, pH 7.0, 0.2 ml. of 10 per cent potassium hydroxide in the center well, 0.2 ml. of 0.05 M substrate or distilled water in the side-arms, and distilled water to the desired volume.

GL: glucose; *P:* pyruvate; *A:* acetate; *S:* succinate; *F:* fumarate; *M:* malate; *KG:* ketoglutarate; *C:* citrate; *E:* endogenous.

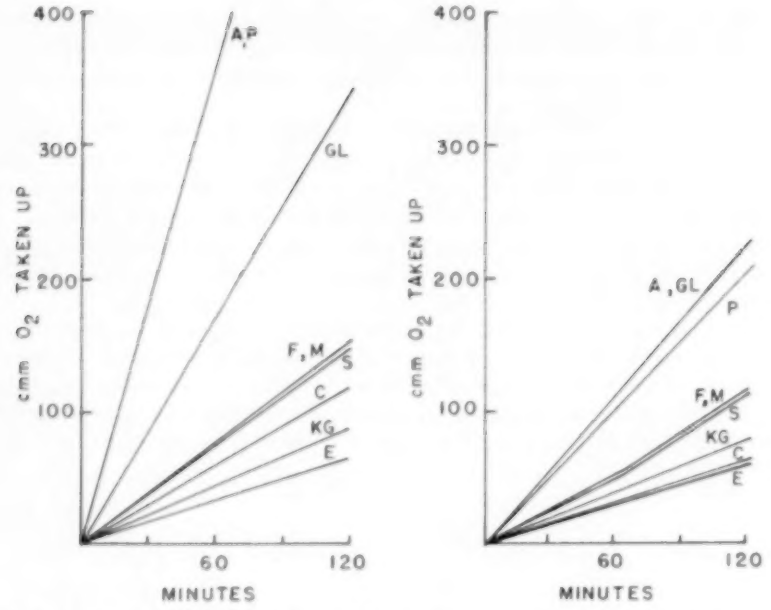

FIG. 2. Oxidation of various intermediates by acetate grown cells of *M. ranae* (SMS) and *Mycobacterium* (607), left and right figures, respectively. Flask contents and legend same as figure 1.

which would seem to indicate that permeability may not be the limiting factor in the apparent failure of this species to oxidize citrate at a significant rate.

It was observed that the rate of acetate oxidation exceeds that of glucose in *M. ranae* (SMS). In *M. ranae* (SMD) and *Mycobacterium* 607, the rates of acetate oxidation were much slower than those of glucose. When the streptomycin-dependent strain of *M. ranae* was grown on the citrate medium, a pattern of oxidation rates for the intermediates not unlike that of the parent strain was present, and the rate of acetate oxidation again exceeded the rate of glucose oxidation.

There existed the possibility of the oxidation of acetate via its methyl group to glycolic and glyoxylic acids. While these compounds are apparently oxidized by *M. ranae* (SMS) and *Mycobacterium* 607, there was no significant increase in the rates of oxidation of these compounds when the cells were grown on the acetate medium (table 1). This observation and the relatively slow rates of oxidation of these compounds would seem to indicate that acetate is not oxidized via this pathway in the microorganisms used in this study.

DISCUSSION

The rapid oxidation of intermediate compounds has been suggested by Krebs (14) as evidence for the participation of a particular metabolic cycle. Stanier (8) has found that the adaptation of a microorganism to a particular substrate

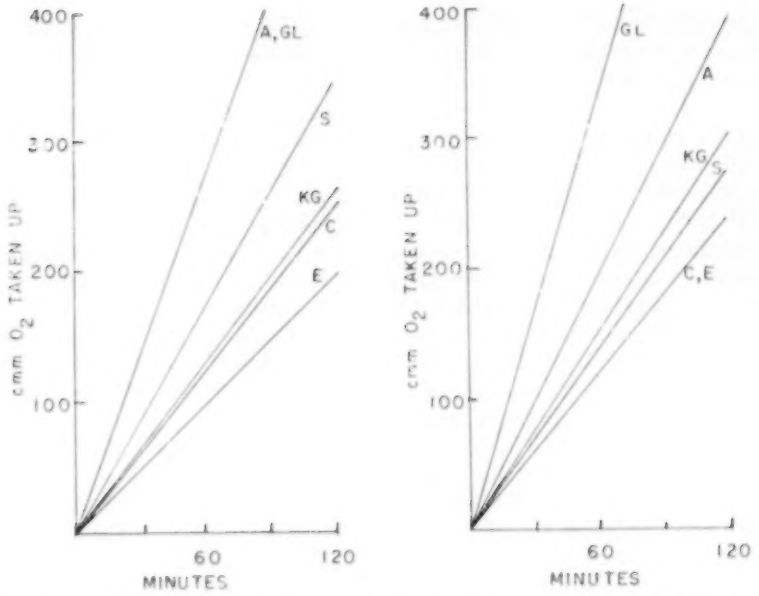

FIG. 3. Oxidation of various intermediates by dried-cell preparations of glucose-grown *M. ranae* (SMS) and *Mycobacterium* 607, left and right figures, respectively. Flask contents and legend same as figure 1.

TABLE 1

OXIDATION OF ACETATE, GLYCOLATE, AND GLYOXYLATE

Organism	Carbon Source in Medium	Cu. Mm. of Oxygen per 60 Min.			
		5 Mg. Dry Wt. Bacilli			
		A	GY	GX	GL
M. ranae (SMS)	Glucose	200	30	25	140
	Acetate	325	50	35	150
Mycobacterium 607	Glucose	60	33	30	340
	Acetate	140	25	25	280

Endogenous values have been subtracted from all of these figures.
A: acetate; *GY:* glycolate; *GX:* glyoxylate; *GL:* glucose.

produces simultaneous adaptation to all of the intermediates involved in the dissimilation of that substrate. An objection to the use of this technique when the metabolic responses are not strictly "adaptive" in nature may be raised. Ajl (15) suggests, however, that, if proper precautions are taken so that the experiments are completely analogous, an increase in the enzymatic response to certain intermediates may be interpreted as evidence for the participation of the particular intermediates in metabolic sequences.

The simultaneous adaptation experiments offer a confirmation of the reports, suggesting the participation of a tricarboxylic acid cycle in the terminal respiration of some acid-fast bacilli. Comparable rates of oxidation of the intermediates of this pathway, regardless of the carbon sources which were used in the medium, can be interpreted as an indication of a tricarboxylic acid cycle in the streptomycin-susceptible strain of *Mycobacterium ranae*. An increase in the rates of the dicarboxylic acids but not alpha ketoglutaric or citric acids by acetate-grown cells of *Mycobacterium* 607 and the streptomycin-dependent strain of *Mycobacterium ranae* may indicate that this is not the major pathway for the oxidation of acetate in these species.

When the streptomycin-dependent strain of *Mycobacterium ranae* was grown on the citrate medium, the pattern of oxidations of the tricarboxylic acid cycle intermediates was similar to that of the parent strain. This would seem to offer further evidence for the interference of streptomycin with terminal respiration, suggesting a possible shift to an alternate pathway in strains of different streptomycin susceptibility. This possibility deserves further investigation with respect to the possible mode of action of the drug.

Lara and Stokes (16) have found that there is an apparent impermeability of the cells of *Escherichia coli* to citrate. These investigators have been able to demonstrate the oxidation of this compound by employing dried-cell preparations. After the cells of *Mycobacterium* 607 and *M. ranae* (SMS) were dried over P_2O_5, the relative rate of citrate oxidation was increased in only the latter species.

Ajl (17) has discussed the possibility of the oxidization of acetate via its methyl group to glycolic and glyoxylic acids. The simultaneous adaptation experiments did not indicate that acetate is oxidized in this manner in either *Mycobacterium* 607 or *M. ranae*.

SUMMARY

On the basis of simultaneous adaptation experiments, further evidence is presented for the participation of a tricarboxylic acid cycle in terminal respiration of some acid-fast bacilli.

Evidence is also presented for the possible participation of a Thunberg-Knoop cycle in *Mycobacterium* 607 and the streptomycin-dependent strain of *Mycobacterium ranae*; however, the involvement of citrate and other compounds in the pathway(s) of oxidation of acetate is not excluded by these experiments. The effect of streptomycin on a possible shift in the pathway of terminal respiration is discussed.

SUMARIO

Estudios del Metabolismo de las Bacterias Acidorresistentes: II. Indicaciones de las Vías Intermedias de la Oxidación del Acetato

A base de experimentos simultáneos de adaptación, apórtase nueva prueba de la participación de un ciclo de ácido tricarboxílico en la respiración terminal de algunos bacilos ácidorresistentes.

También se presentan datos relativos a la posible participación de un ciclo de Thunberg-Knoop en el *Mycobacterium* 607 y en la cepa estreptomicino-dependiente del *Mycobacterium ranae*; sin embargo, no excluyen estos experimentos la intervención del citrato

y de otros compuestos en la vía (o vías) de oxidación del acetato. Se discute el efecto de la estreptomicina sobre una posible desviación en la vía de la respiración terminal.

RESUME

Etude sur le métabolisme des bactéries acido-résistantes: II. Les signes d'une voie intermédiaire de l'oxydation de l'acétate

Sur la base d'expériences d'adaptation simultanées, les auteurs présentent d'autres preuves de la participation d'un cycle tricarboxylique au terme des échanges gazeux chez certains bacilles acido-résistants.

Il est également fourni des données sur la participation possible du cycle Thunberg-Knoop dans le *Mycobacterium* 607 et la souche streptomycine-sensible du *M. ranae*; toutefois, le rôle du citrate et autres composés dans la voie, ou les voies d'oxydation de l'acétate n'est pas réfuté par ces expériences. L'action de la streptomycine sur une dérivation possible de la voie des oxydations terminales est commentée.

Acknowledgment

The writers wish to thank Dr. Emil Bogen of Olive View Sanatorium, Olive View, California, for his encouragement and advice with respect to numerous aspects of this work.

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DECONTAMINATION OF ARTICLES MADE BY TUBERCULOUS PATIENTS IN PHYSICAL MEDICINE AND REHABILITATION[1]

A Study Using Carboxide® Gas

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INTRODUCTION

Decontamination of articles made or used by tuberculous patients while participating in occupational therapy or manual arts therapy in physical medicine and rehabilitation has presented a difficult problem for many years. Heat with or without moisture is the method of choice for rendering tubercle bacilli nonviable. Heat, however, is injurious to many types of materials. Glycol vapors have been awarded a certain degree of success in the disinfection of air but are not effective on surfaces. The use of ultraviolet light is impractical because of its low penetrating power and the difficulty of direct exposure of the entire area of an article. A single technique which can safely and effectively be applied to a variety of materials would be of great usefulness.

Gaseous disinfection appears to be ideally suited to this purpose providing it is sufficiently destructive to tubercle bacilli. Formaldehyde has been employed for other microorganisms but, as used in the present studies, it was somewhat undependable for tubercle bacilli. Gaseous ethylene oxide has been suggested for sterilization by Phillips and Kaye (1, 2, 3), who have thoroughly reviewed the literature on its use as a disinfectant and fumigant (4). They have studied its effectiveness on a number of organisms, mainly the spore former *B. globigii*, which they consider one of the most difficult organisms to kill. Brief studies were also made with BCG and *Mycobacterium phlei*. Kaye (5) has also reported effective disinfection with Carboxide,[3] a nontoxic, nonexplosive, noninflammable mixture of 10 per cent ethylene oxide and 90 per cent carbon dioxide. These reports have led the present writers to test the efficacy of Carboxide® in rendering virulent tubercle bacilli nonviable and to determine whether it has any detrimental effect on the various materials used in physical medicine therapy programs.

MATERIALS AND METHODS

An apparatus similar to that used by Kaye (5) was assembled and has been used for more than four years at this hospital. The exposure chamber was a standard autoclave with an inside diameter of 20 inches and length of 36 inches, built to withstand a pressure of at least

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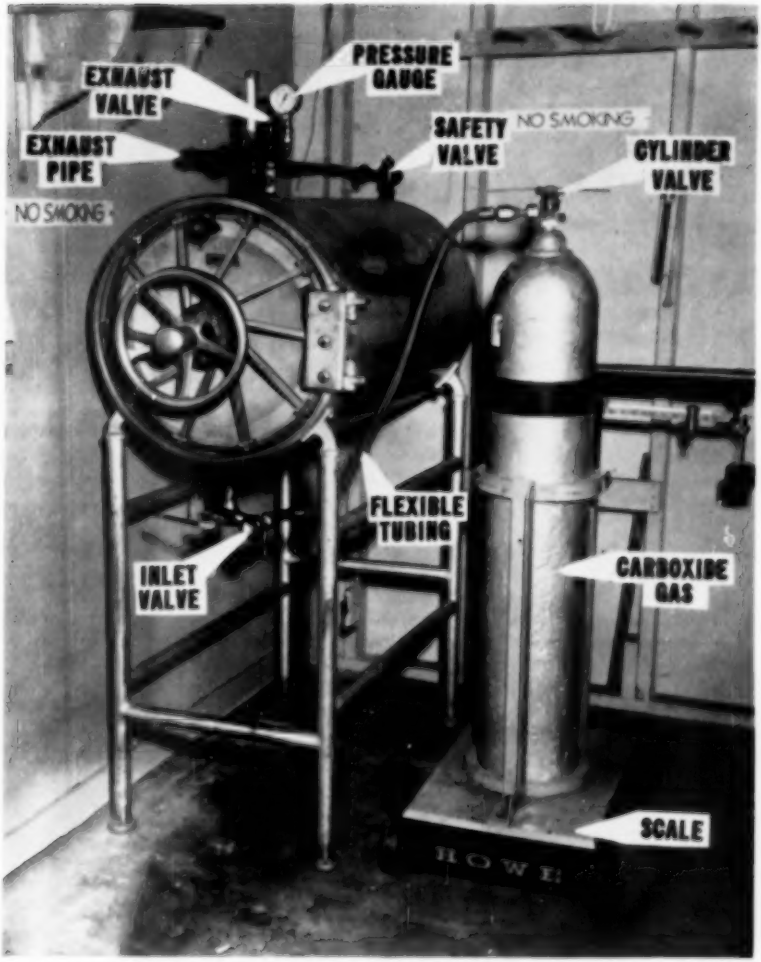

FIG. 1. Decontamination chamber showing Carboxide® gas cylinder, weighing scale, and operating controls.

40 pounds, which allowed a 100 per cent factor of safety, as exposures were made at 20 pounds. A safety valve on the top of the chamber was set for 30 pounds. A removable tray was fitted into the chamber so that the articles did not rest directly on the floor of the autoclave. A cylinder of Carboxide® gas (30 or 60 pounds net gas content) was connected to the inlet valve on the bottom of the autoclave by means of high-pressure flexible tubing and fittings. The cylinder was fastened firmly on a standard platform scale, as it has been found convenient to use weight rather than pressure gauges for measuring gas consumed. Following the decontamination process, exhaustion of the gas from the chamber was made through a pipe leading to the outside air (figure 1). The entire system was tested carefully under 45 pounds of gas pressure for leaks before being used.

Employing this chamber, preliminary bacteriologic studies indicated a superiority of Carboxide® to formaldehyde in rendering suspensions of tubercle bacilli nonviable. Formaldehyde gas, as used in these studies, failed to kill as few as 0.001 to 0.01 mg. (wet weight) of bacilli in as small a volume as 0.1 ml. of 1 per cent beef serum water. Carboxide®, using an initial pressure of 20 pounds without evacuation, consistently rendered noncultivatable suspensions of 2 mg. or less of several strains of tubercle bacilli. The strains included fresh isolates as well as old laboratory strains. The sterilizing effect continued until a cylinder of Carboxide® was evacuated to approximately 20 per cent of its original weight. If exposed organisms were in "dry" clumps of approximately 1 mm. in diameter obtained from solid egg slants, however, bacilli were often viable. This indicated that either the large clumps of tightly packed organisms or the lack of moisture was a factor. Consequently, experimental tests were modified to simulate more closely conditions which might obtain on accidentally contaminated articles. The following technique was worked out.

Sputum specimens were selected for their high content of tubercle bacilli as revealed by microscopy of untreated, unconcentrated specimens. From 0.05 to 0.1 ml. was deposited on small sterile linen strips in the bottom of sterile metal-capped test tubes and dried at room temperature for seventy-two hours. Metal caps were then replaced by tight cotton stoppers to test the penetrating power of the gas. At this time, more tubes of each sputum specimen were similarly prepared for testing without drying. Half the strips of each specimen were exposed for twenty hours, the initial pressure being 20 pounds; the remainder were held as unexposed controls. Cylinders of Carboxide® were at least half full for all of these experiments for reasons subsequently discussed.

Upon removal from the chamber, cotton stoppers were replaced with metal caps. After moistening each specimen with 0.1 ml. of sterile water to prevent further damage from drying, the tubes were maintained at 37° C. for twenty-four hours to permit escape of possible trapped bacteriostatic quantities of gas (6). It was found that ordinary microorganisms in sputum, particularly yeasts, were often refractory to killing by Carboxide® when dried in this manner. Both exposed and unexposed samples were therefore treated with alkali, centrifuged and washed, and sediments were cultured on liquid as well as on at least two types of solid medium.

Dried test specimens had to be comparatively large for successful cultivation from unexposed controls, without which negative results with exposed material would be meaningless. Ten to 12 dried specimens were pooled before alkali treatment. In spite of the use of ten to twelve times as much material, growth on 4 of the 8 dried controls was less than that from corresponding moist controls, indicating a certain degree of injury by drying.

RESULTS

Satisfactory tests were obtained with 12 sputum specimens. Tubercle bacilli were recovered from unexposed aliquots, both dried and moist, of 8 of these 12 specimens. Low recovery was undoubtedly due to the use of small quantities of sputum. In all of the 8 cases, bacilli were noncultivatable after exposure if they were moist when exposed. If dried, bacilli in 6 of the 8 specimens were noncultivatable subsequent to exposure; the remaining 2 sputum specimens yielded viable tubercle bacilli.

CONDITION OF SPUTUM DURING EXPOSURE

Number of:	Dry	Moist
Positive controls	8	8
Negative exposed	6	8
Positive exposed	2	0

The number of bacilli on articles accidentally contaminated by patients would probably be only a fraction of the number used experimentally in order to obtain growth of dried control specimens. Noncultivatability of 75 per cent of exposed dried specimens containing comparatively tremendous numbers of tubercle bacilli appeared to indicate that dried organisms were frequently susceptible to Carboxide®.

Technique

Prior to using the decontamination chamber, make certain that the chamber door when closed will be absolutely gas-tight and that high-pressure flexible tubing and fittings are used to connect the cylinder of Carboxide® gas to the chamber.

The technique used for decontamination of articles handled by tuberculous patients has been as follows:

1. Articles were placed on the removable tray in the chamber and completely covered with a small rug or scarf to prevent their being blown about when gas was released into the chamber.
2. Door of chamber was carefully closed and locked.
3. Exhaust valve on chamber was closed.
4. Inlet valve on chamber was opened.
5. Valve of Carboxide® cylinder was quickly and completely opened until pressure in the chamber read 20 pounds; then was quickly closed.
6. Exhaust valve on the chamber was then opened and gas was permitted to escape until the pressure gauge read 1 to 2 pounds.
7. Exhaust valve on chamber was again closed.
8. Step 5 was repeated. (Steps 4 to 6 served to flush existing air out of chamber before filling with the toxic gas.)

After twenty to twenty-four hours, the chamber was emptied in the following manner:

1. Chamber exhaust valve was opened wide to permit escape of all gas to the outside.
2. When pressure gauge read 0, chamber door was opened, articles were removed and placed in paper bags marked with the patient's name, ward number, and the name of the article, thus avoiding further contamination.

The precautions to be observed in using Carboxide® for decontamination are as follows:

Condensed gas (liquid) should not come into contact with articles in the chamber, as it may cause damage to some materials. Liquid, if any, accumulated in the bottom of the chamber; the tray on which articles were placed served adequately to keep them above level of liquid.

Reasonable care must be exercised to avoid breathing the gas. In high concentrations, ethylene oxide is an intolerable irritant to eyes, nose, and throat. Prolonged inhalation of even slight concentrations of Carboxide® should be avoided, as it may result in greater susceptibility to future doses. A toxic concentration of ethylene oxide in the body may be indicated by any or all of the following symptoms: headache, dizziness, generalized weakness, shakiness or heavy feeling, difficulty in walking or standing, nausea, vomiting, fainting, or unconsciousness.

The period of exposure should last for twenty to twenty-four hours.

The cylinder from which the chamber is filled should be at least one-third to one-half full of gas.

The last-named precaution requires some comment. If 60-pound cylinders had already been intermittently evacuated, as in the present usage, to approximately 12 to 14 pounds (or 30-pound cylinders to 6 to 8 pounds), the remainder of the gas was evidently nontoxic to tubercle bacilli in suspension, in contrast to gas from full cylinders. This point was checked with three different cylinders. The logical reason for failure at this point was that the toxic fraction of the mixture (ethylene oxide) according to Phillips and Kaye (1, 4) was exhausted more rapidly than the gas responsible for the pressure and remaining weight. According to experts in the company which supplied the gas, intermittent use and gradual evacuation, such as occurs with small exposure chambers, might result in incomplete mixing of the two gases. It was their opinion that ethylene oxide would be discharged in considerable amounts until approximately 20 per cent of the gas remained. For a wide margin of safety, the present writers have advised replacing a cylinder after about one-half to two-thirds of a cylinder has been used; that is, when a 60-pound cylinder has been reduced to 20 to 30 pounds, or a 30-pound cylinder to 10 to 15 pounds. The 60-pound cylinder has been used in all of the experiments. This cylinder can safely be used for twenty to twenty-five decontaminations, each costing approximately 70 cents. At this hospital, approximately twenty articles are decontaminated at one time, making the average cost 3.5 cents per article. As an additional factor, this method also is less time-consuming than the usual methods of decontaminating individual articles as one therapist can handle the entire procedure in approximately ten minutes.

DISCUSSION

Advantages of the use of Carboxide® in decontamination are obvious. Exposure of physicians and therapists to toxic fumes is nil with the proper use of a well-assembled apparatus. The gas is harmless to articles exposed. It is highly diffusible and permeable. It airs out readily without residual odor, stain, or oily deposit. It rendered noncultivatable as much as 2 mg. of tubercle bacilli of various strains suspended in water containing 1 per cent beef serum. Formalin solution, on the other hand, volatilized from potassium permanganate crystals often failed to kill as few as 0.001 to 0.01 mg. of tubercle bacilli suspended in the same medium.

Carboxide® was apparently also toxic for tubercle bacilli in small volumes of sputum. If the specimen was moist when exposed, bacilli were more consistently rendered noncultivatable than if previously dried. However, tubercle bacilli in 75 per cent of the dried specimens were also noncultivatable after exposure.

Kaye and associates (4, 9) have also indicated the advisability of moisture for disinfection. They found that complete drying, such as that which occurred with prolonged evacuation before the admission of ethylene oxide, made difficult the killing of spores of *B. globigii*, especially if the suspending medium contained

salts. Deliberately contaminated antimicrobial drugs dried by lyophilizing, however, were sterilized by exposure to ethylene oxide (9). On the other hand, high relative humidity of the surrounding atmosphere interfered with sterilization by ethylene oxide; a decrease in relative humidity from 100 to 28 per cent increased the speed of killing of spores (4).

These points raised the question in the present work whether the 2 dried sputum specimens from which tubercle bacilli were recovered after Carboxide® exposure had, for some reason, been more completely dried than had the other 6. None of the present experimental work affords an answer to that question. It appears unlikely, however, that drying would have been as complete as it is under prolonged vacuum. The degree of dryness of specimens as well as of surrounding atmosphere, degrees of susceptibility of different strains of the organism, differences in the chemical composition of the sputum, differences in the actual numbers of tubercle bacilli exposed, and many other factors may be of importance in the degree of resistance to injury by Carboxide® gas.

It was found that tubercle bacilli did not always survive simple drying procedures. In preliminary work it has been found that, in 3 of 10 strains, drying in 0.1 ml. of 1 per cent aqueous beef serum sufficed without other treatment to render noncultivatable as much as 2 mg. of bacilli in twenty-four hours at 37°C. Moreover, it was necessary to use ten to twelve times as much dried as moist sputum to obtain growth from unexposed controls, which even then was meager compared with that of corresponding moist specimen controls.

Lack of toxicity of Carboxide® gas to tubercle bacilli at low weight levels in cylinders, in spite of high pressures readily attained in the exposure chamber, contrasts with the claim of Eisman (8) that toxicity of Carboxide® for *E. coli* and *S. aureus* is due largely to the combined effects of carbon dioxide and pressure rather than to ethylene oxide.

Although guinea pig inoculation might have appeared to be more convincing evidence of the state of viability of these organisms after exposure, modern culture methods permit detection of a small number of strains which do not infect guinea pigs (7). The reverse is also true in a small number of cases, but it has no bearing on the present work inasmuch as positive cultures resulted from all unexposed controls. The evidence is clear-cut that Carboxide® was consistently effective on two hundred to two thousand times as many organisms in wet suspension as was formaldehyde under the conditions of these experiments. Drying in itself proved somewhat injurious to the viability of tubercle bacilli. It appears probable that the combined effects of drying and exposure to Carboxide® may suffice to render harmless the small numbers of tubercle bacilli which might be present on articles handled by patients. In the absence of more certain methods of decontamination, it would seem that the use of Carboxide® is indicated.

SUMMARY

A decontamination procedure for articles handled by tuberculous patients utilizing the nonexplosive, noninflammable gas, Carboxide®, has been described.

Bacteriologic studies with virulent tubercle bacilli indicated the consistent toxicity of the gas to tubercle bacilli in suspension in serum water and in small volumes of moist sputum, and a somewhat less consistent toxicity to organisms in dried sputum. Drying alone is somewhat injurious to tubercle bacilli.

Carboxide® has proved harmless to many types of materials and to personnel when used properly in well-designed apparatus. The following types of material have been exposed to this gas without detrimental effect: leather, wool, cotton, rayon, silk, felt, nylon, paper (including books and cardboard), plastic, wood, straw, oil and water color paintings, pottery, metals, semiprecious stones, linoleum, cellophane, metallic textiles, and rubber.

It is believed that, until more perfect methods of decontamination are available, the use of Carboxide® in this manner is indicated for articles made and used by patients with infectious tuberculous lesions. Further investigation is being considered in order to ascertain if similar results can be obtained by using less weight of gas in the decontamination chamber and shorter periods of exposure, thereby resulting in a more economical procedure. Consideration is being given to the construction of a decontamination room large enough to accommodate therapy carts.

SUMARIO

Descontaminación de los Artículos Fabricados por Tuberculosos en Obras de Medicina Física y Rehabilitación: Estudio con el Uso de Gas Carbóxido®

Descríbese un procedimiento de descontaminación de artículos manipulados por tuberculosos que utiliza el gas inexplosible e ininflamable, Carbóxido®.

Los estudios bacteriológicos con bacilos tuberculosos virulentos indicaron la constante toxicidad del gas para los bacilos tuberculosos suspendidos en agua sérica y en pequeños volúmenes de esputo húmedo y una toxicidad algo menos constante para los microbios en el esputo desecado. La desecación sola es algo nociva para los bacilos tuberculosos.

El Carbóxido® se ha mostrado inocuo para muchas clases de substancias y para el personal cuando se usa debidamente en aparatos bien construídos. Substancias de las siguientes clases han sido expuestas al gas sin efecto perjudicial: cuero, lana, algodón, rayón, seda, fieltro, nilón, papel (incluso libros y cartón), plásticos, madera, paja, cuadros al óleo y acuarelas, alfarería, metales, piedras seniprecíosas, hule, celófano, telas metálicas y caucho.

Parece que, hasta que se cuente con métodos más perfectos de descontaminación, está indicado el uso del Carbóxido® en esta forma para los artículos fabricados y usados por enfermos que tienen lesiones tuberculosas abiertas. Se tienen en consideración investigaciones ulteriores con mira a averiguar si pueden obtenerse resultados semejantes usando menos peso de gas en la cámara de descontaminación y períodos más cortos de exposición, consiguiendo así un procedimiento más económico. También se presta consideración a la construcción de un cuarto de descontaminación de tamaño suficiente para acomodar carros de terapéutica.

RESUME

Désinfection des objets manufacturés par les malades tuberculeux dans les centres de physiothérapie et de réadaptation: Etude effectuée avec le Carboxide® à l'état gazeux

Description d'un procédé de désinfection des objets manipulés par les malades tuberculeux utilisant le Carboxide®, gaz non explosif, non inflammable.

Des recherches bactériologiques avec des bacilles virulents démontrent la toxicité constante du gaz pour les bacilles tuberculeux en suspension dans le sérum physiologique et dans un petit volume de crachat humide, et une toxicité un peu moins constante pour les bacilles renfermés dans le crachat sec. Le séchage, à lui seul, altère un peu le bacille de Koch.

Le Carboxide® se montre inoffensif pour de nombreuses catégories de matières ainsi que pour le personnel, quand il est utilisé de façon appropriée à l'aide d'un appareil convenable. Les diverses matières ayant été exposées sans inconvénients à l'action de ce gaz sont les suivantes: cuir, laine, coton, rayonne, soie, feutre, nylon, papier (y compris les livres et les boîtes de carton), matières plastiques, bois, paille, peintures à l'huile ou à l'eau, poterie, métaux, pierres semi-précieuses, linoléum, cellophane, textiles métalliques, caoutchouc.

Les auteurs estiment que, jusqu'à ce que l'on dispose de procédés plus parfectionnés, l'usage du procédé au Carboxide® est indiqué pour les objets manufacturés ou utilisés par le tuberculeux porteur de lésions ouvertes. Une nouvelle investigation est envisagée, en vue de vérifier si des résultats semblables ne pourraient être acquis en réduisant le poids du gaz dans la salle de désinfection et la durée de l'exposition au gaz, ce qui rendrait le procédé plus économique. La construction d'une salle de désinfection assez grande pour permettre d'y placer les chariots affectés aux traitements est envisagée.

Acknowledgment

The writers are indebted to Yaye Furutani and Adeline Hess for their splendid cooperation in the bacteriologic investigative work; to the personnel on the Physical Medicine and Rehabilitation Service, especially Virginia Niles, O.T.R. Chief, Occupational Therapy Section, and Lillian Perlstadt, O.T.R. (since November 1953, Chief, Occupational Therapy, Veterans Administration Research Hospital, Chicago) for their valuable assistance; to the Medical Illustration Laboratory for its excellent photographs; and to the Engineering Service for the modifications and installation of the decontamination chamber.

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Case Reports

PLEURAL MESOTHELIOMA[1]

Report of Four Cases

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The purpose of this paper is to report 4 cases of pleural mesothelioma treated by the writers. At one time, various terms such as fibroma, endothelioma, fibrosarcoma, sarcoma-like tumor, giant sarcoma of the pleura, and endothelial sarcoma were applied to these pleural tumors. Robertson (1) believed that the diagnosis of a primary pleural neoplasm was ill-defined and too freely made. He laid down rigid requirements which tended to limit the usage of this terminology.

CASE REPORTS

Case 1 (ORH, 7052). The patient was admitted complaining of chest pain which had been intermittently present during the preceding year. There was no weight loss, loss of appetite, or cough. He was a well-developed, well-nourished, 61-year-old white male in no distress. The chest was essentially normal on physical examination. The blood pressure was 140 systolic and 80 diastolic in mm. of mercury, and his heart was normal to auscultation.

Blood counts, urinalysis, and a serologic test for syphilis were all reported as normal. The chest roentgenograms showed an opacity in the left lower lung field (figure 1). The skull roentgenograms were normal, as were the intravenous pyelograms.

While in the hospital the patient had a thoracotomy, and a mesothelioma of the pleura was excised (figure 2). His postoperative course was satisfactory, and he was sent home on leave pending completion of hospital treatment for thirty days.

Pathologic Report

Gross: The specimen consisted of an encapsulated tumor which measured 5.5 by 4.5 by 1.0 cm. with an attached pedicle 1.0 cm. in length. A small fragment of the lingula was removed with the mass. The surface of the tumor was smooth and glistening and appeared to be covered by a thin serosal membrane. On section, the tissue was gray and homogeneous with a lobular texture and varied in consistency from moderately firm to soft and friable (figure 2).

Microscopic: Sections stained with hematoxylin and eosin showed abundant thick collagen fibers running in parallel bundles. Interspersed between the collagen fibers were scattered elongated cells having a spindle-shaped nucleus. The cells were uniform in size and shape and were rather widely separated. There were no mitoses evident. In some areas there was a more cellular component, with the tumor cells becoming more plump and having a rounded to oval nucleus with sparse chromatin. A section taken through the point of attachment to the lung showed dense hyalinization of the pleura, with serosal cells lining irregular spaces. Reticulin stain (Wilder) revealed thin reticulin fibers surrounding the tumor cells and scattered throughout the more acellular portions (figure 3).

Final diagnosis: Mesothelioma of pleura, benign.

[1] From the Department of Surgery and the Department of Pathology, University of Washington School of Medicine, and the Seattle Veterans Administration Hospital.

FIG. 1. ORH, 7052, *Case 1*. The chest roentgenogram shows a discrete mass in the left lower lung field.

Case 2 (PEMeC, 11087). Six weeks prior to admission this 48-year-old white male noted the gradual onset of high right thoracic pain associated with pain descending along the inner aspect of the right arm. The pain had slowly increased in severity. No cough or hemoptysis had been present. Two days prior to admission the patient's local doctor noted roentgenographic evidence of a large right upper lobe mass (figure 4).

The findings on physical examination were essentially normal except for dullness over the right superior aspect of the chest, both anteriorly and posteriorly, with bronchial breath sounds over this area, and absence of sweating over the upper right chest and right side of the face.

Sputum studies were negative for acid-fast bacilli, as were the gastric aspirations. Determinations for blood protein, electrolytes, and urea nitrogen yielded normal values. Roentgenographic examination of the chest revealed a large mass in the right apex occupying most of the space usually occupied by the upper lobe. The Quinizarin Compound Test for sweat revealed no evidence of sweating on the right side of the neck, face, and shoulder.

While in the hospital a bronchoscopy and esophagoscopy were done on the patient. Both revealed deviation of the organs examined, slightly to the left. The upper right lobe main stem bronchus was depressed inferiorly. A right thoracotomy was performed with removal of the tumor and the attached overlying ribs (two to five), and a wedge excision

FIG. 2. The gross specimen seen in figure 1

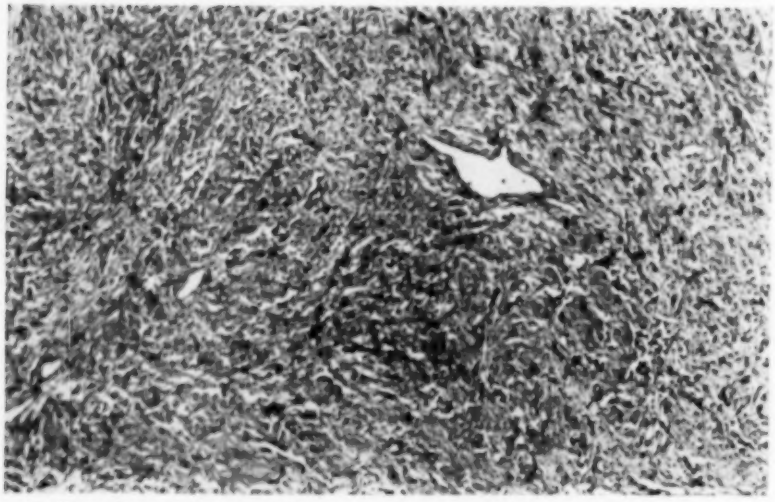

FIG. 3. The microscopic appearance, low-power, of the tumor shown in figures 1 and 2

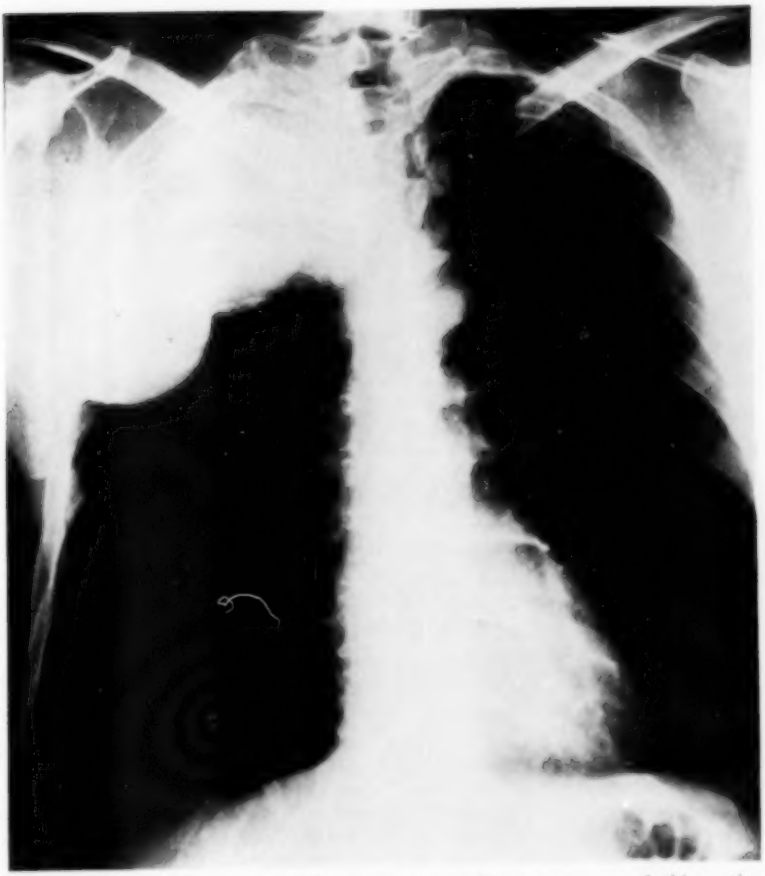

FIG. 4. PEMcC, 11087, *Case 2*. The roentgenographic appearance of this patient's tumor.

of the right upper lobe was done. Two weeks later the patient was sent home on leave pending completion of hospital treatment. He died on May 16, 1954, two months after the thoracotomy operation, with recurrence of the tumor. Autopsy was not permitted.

Pathologic Report

Gross: The specimen was received in multiple fragments, the largest of which measured 2.5 by 1.5 by 0.3 cm. The tumor prior to removal measured approximately 10.0 cm. in diameter. On section, the tumor was soft in consistency and had a uniform light gray color (figure 5).

Microscopic: Sections showed a pleomorphic sarcoma invading the intercostal muscles. The tumor cells were spindle-shaped with oval nucleus and prominent nucleoli. Mitoses were frequent and often of bizarre type. In routinely stained sections there was minimal

FIG. 5. A portion of the tumor and resected rib from *Case 2*

interstitial connective tissue proliferation with tumor cells often lying in parallel bundles. Tumor giant cells having two to three irregular nuclei were occasionally seen. Focal areas of necrosis were noted throughout the tumor. Wilder's reticulin stain revealed fibers encircling the tumor cells. Multiple sections revealed no evidence of lymphatic or blood vessel invasion (figures 6*a* and *b*).

Final diagnosis: Malignant mesothelioma, right thoracic wall, with invasion of right lung.

Case 3 (PRA, 9893). A 33-year-old white male was admitted for study and treatment of a completely asymptomatic lesion involving the right lower lobe noted on a routine chest film in September, 1953. There was no history of respiratory infection, cough, pleuritic pain, or any other symptomatology referable to the respiratory system. The patient weighed 160 pounds and stated that he usually weighed 150 pounds.

The findings on physical examination were essentially normal except for findings in the right chest. Over an area of approximately 5.0 by 5.0 cm. in the anterior axillary line, some dullness and decreased breath sounds were present.

Sputum tests repeatedly performed were found to be negative for acid-fast bacilli. The residual lung volume was 3,687. The albumin-globulin ratio and total protein were normal. The hematocrit was 46 per cent and the thymol turbidity was 0.4 mg. Postero-anterior and right lateral roentgenograms of the chest revealed a large, fairly well-delineated mass in the region of the interlobar fissure approximately two inches above the right costophrenic sinuses. This was considered to represent a tumor, probably one of benign type (figure 7).

The purified protein derivative, coccidioidin, and histoplasmin cutaneous reactions were negative. On December 18, 1953, a bronchoscopy was attempted, but the instrument could not be passed. On December 11, 1953, thoracotomy was done with a block resection of the portion of the right lateral wall, including a pleural tumor. On December 17, 1953, the thoracotomy was reopened, the plastic pleural adhesions were lysed, and multiple excisions of pleural implants were done. Following the thoracotomy, radioactive gold was instilled. The patient had a rather uncomfortable postoperative course, with slight wound infection which was superficial. The patient is feeling symptomatically improved.

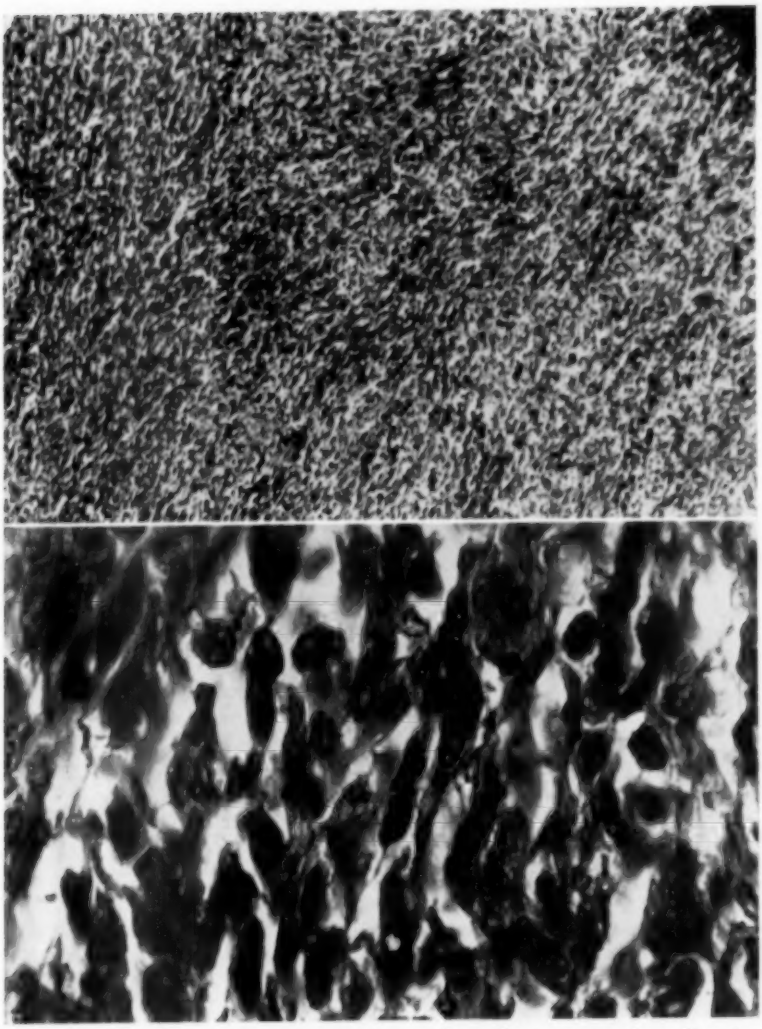

FIG. 6a. (Top) The low-power appearance of the malignant tumor from *Case 2*
FIG. 6b. (Bottom) The high-power view of the same tumor from *Case 2*

Pathologic Report

Gross: The specimen consisted of an irregular mass which measured 9.5 by 6.0 cm. It was firmly attached to the parietal pleura and was removed together with two segments of ribs and intervening intercostal muscle. The surface of the neoplasm was smooth and glistening and had a pinkish-white color. The base of the tumor at the point of attachment to the parietal pleura measured 3.5 by 2.0 cm. The cut surface had a variegated appear-

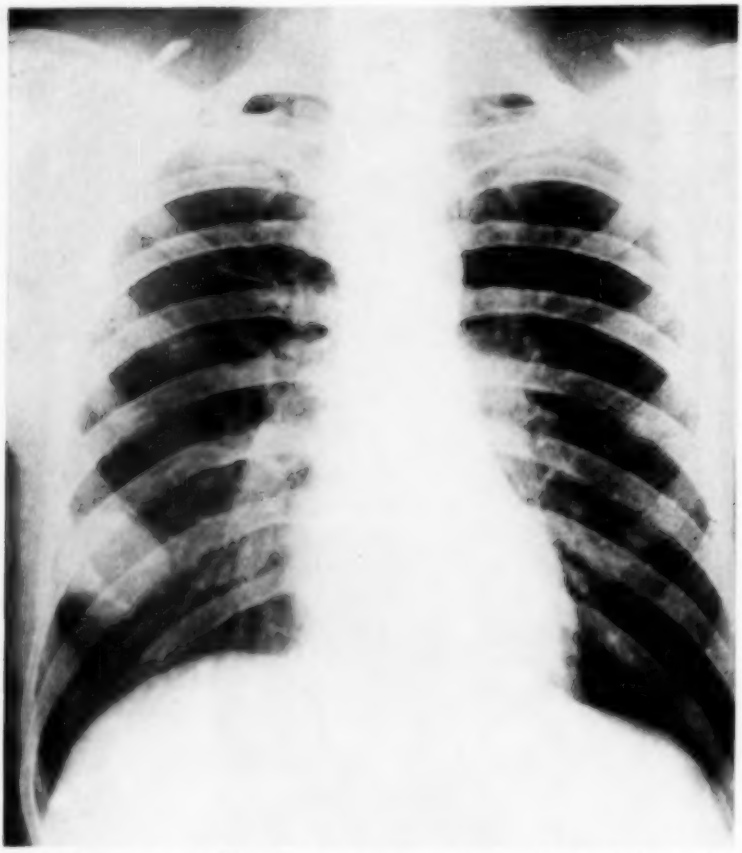

FIG. 7. PA, 9893, *Case 3*. The chest roentgenogram shows a discrete lesion in the right lower lung field.

ance, with the majority of the tissue appearing pale yellowish-gray. Hemorrhagic and necrotic foci were seen throughout the tumor; however, they appeared to be somewhat more prominent at the base. Small areas of cystic degeneration up to 0.5 cm. in diameter were evident (figure 8).

Microscopic: Sections revealed a cellular tumor consisting of solid masses of plump cells having a large oval to round nucleus and abundant eosinophilic cytoplasm. Mitoses were scattered rather uniformly throughout the tumor. Sections taken at the base showed tumor cells invading the intercostal spaces. Vascularity was not prominent, and the tumor was well preserved. Sections of the pleural implants had a similar histologic appearance. Wilder's reticulin stain revealed scant reticulin fibers scattered throughout the tumor (figures 9*a* and *b*).

Final diagnosis: Solitary malignant mesothelioma with multiple pleural implants.

Case 4 (CW). Approximately one week prior to admission, the patient, a three-year-old white girl, contracted a cold followed by a sore throat with fever as high as 103° F. The

FIG. 8. The gross specimen removed at the first operation, from *Case 3*

fever continued. There was no vomiting, but regurgitation occurred with coughing. Dyspnea, at times severe, gradually developed. There was a complaint of abdominal pain one day prior to entry. There was no marked diarrhea, but loss of appetite had occurred for two days. She took liquids well. The urinary output had decreased in the last two days.

Physical examination revealed the heart apex impulse in the right midclavicular line. There was a harsh, rasping, apical, systolic murmur. Percussion of the entire left lung field was dull. There were diminished breath sounds over the left side, with loud rasping breath sounds over the right lung field.

On June 20, 1951, a chest film showed a dense opacity involving the entire left chest. The heart, mediastinum, and trachea were displaced markedly to the right. The diaphragm was not identified on the left. The right lung fields appeared clear. The findings were interpreted as representing a massive pleural effusion on the left side.

A left thoracotomy was performed. The entire left pleural space was filled with a thick, gelatinous, and degenerating tumor containing small lobules of dark brown bloody fluid. On July 15, 1951, the patient died.

Pathologic Report

Gross: A fleshy white neoplasm completely filled the left hemithorax. The neoplasm pushed the heart and great vessels far to the right and obscured the left lung completely from view. The neoplasm was easily separated from the underlying bony framework of the thoracic wall. At times the cleavage line between thoracic viscera and tumor was difficult to determine; however, there was no evidence of invasion of the lung or other thoracic structures. At autopsy, the tumor was found only in the left thoracic cavity.

Microscopic: The sections revealed a malignant neoplasm composed of closely packed polyhedral and spindle-shaped cells. Tumor giant cells were seen frequently throughout the sections. Stroma was minimal and appeared quite vascular. There was no evidence of

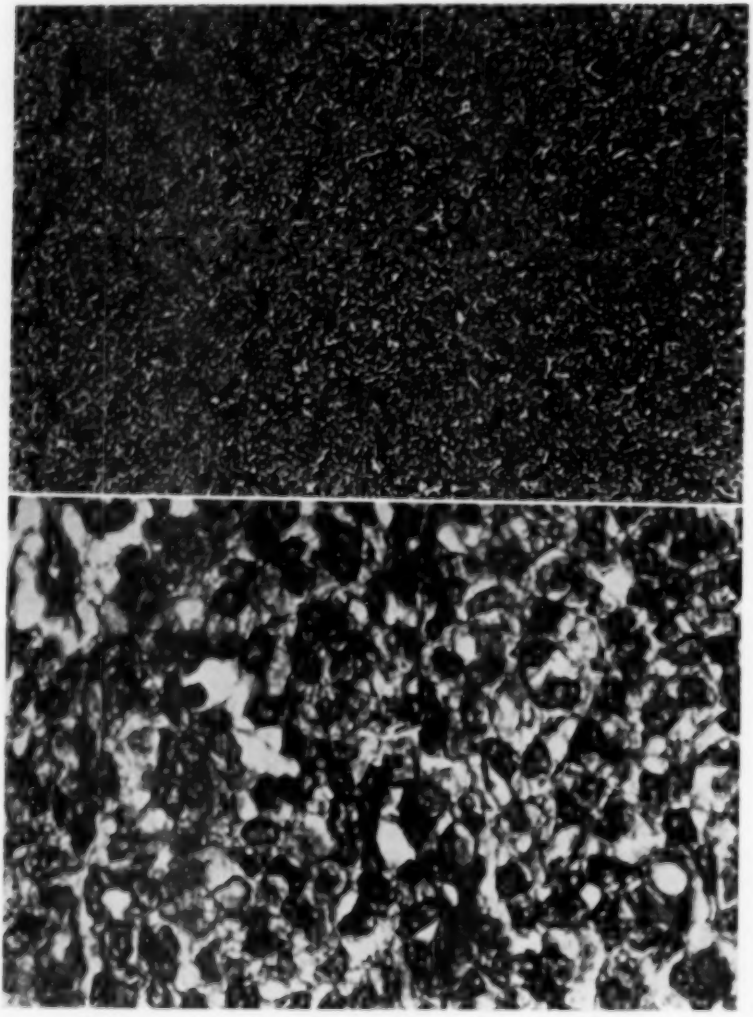

FIG. 9*a*. (Top) The low-power view of the tumor in *Case 3*
FIG. 9*b*. (Bottom) The high-power view of the tumor in *Case 3*

osteoid or new bone formation. Multiple sections of the left lung revealed patchy areas of atelectasis due to compression of the overlying tumor.

Final diagnosis: Diffuse malignant pleural mesothelioma.

COMMENT

At the present time primary pleural neoplasms are the subject of renewed interest and controversy in recent literature. In 1942, Stout and Murray (2) reported a case of a malignant pleural tumor composed of spindle-shaped cells with reticulin fibers between the cells and prominent vascularity. When the malignant tumor cells were cultured *in*

vitro, they displayed the characteristics of mesothelium and the tumor was believed to be a mesothelioma. The mesothelial cell is a simple, flattened cell layer which covers the surface of all serous cavities (pleural, pericardial, and peritoneal). The surface of the protoplasm is provided with a thin, condensed, crustlike layer which sometimes has a distinct brush border. The surface of the flattened, round, or oval nucleus is slightly excavated and occasionally there is a diplosome with a central flagellum protruding into the serous cavity. All such layers of squamous cells when treated with silver nitrate will show the typical mosaic of block cell limits (Maximow) (3).

The prospective potencies of mesothelial cells are twofold—epithelial and fibroblastic. In tissue cultures, mesothelium of mammals may show for a time a purely epithelial type of growth in islands and sheaths of polyhedral flattened cells. In inflammation, mesothelial cells after a period of contraction and rounding off give rise to typical fibroblasts. This also occurs in tissue culture.

The presence of a mesothelioma of the pleura should be suspected in all patients having rheumatic symptoms which are associated with a circumscribed intrathoracic tumor. Pricolo and Lomonaco (18) emphasize the joint symptom as the basis for the diagnosis of this tumor, particularly the swelling and pain in the joints of the hand, hip, elbow, and back. In some cases there is an elevation of temperature. It is noted that the bronchoscopic, bronchographic, and cytologic reports are not as important here as in other tumors involving the lungs.

Primary pleural mesotheliomas are divided into two main groups: the diffuse and the localized. The diffuse form usually produces widespread thickening of the pleura covering the lung, diaphragm, pericardium, and thoracic wall. The tumor invades the underlying tissues superficially and usually does not metastasize; however, it may in rare instances metastasize to regional lymph nodes or distant foci. The solitary tumor is usually sharply circumscribed, pedunculated, and often projects into the pleural cavity. The lung or soft tissues of the thoracic wall may be indented. The benign solitary tumors grow slowly and may reach a large size before being discovered. The malignant tumors have a broad attachment to the pleura and infiltrate the tissues of the chest wall or lung. Frequently they appear grossly circumscribed; however, on microscopic section they usually show invasion. Microscopically, the benign tumors are composed of spindle-shaped cells similar to a fibroblast. These cells are interspersed between variable numbers of thick and thin collagen fibers. The degree of cellularity may vary in different tumors as well as in different portions of the same tumor. The malignant tumors are much more cellular, with reticulin fibers and small numbers of collagen fibers interspersed between the tumor cells. There is considerable variability in the amount of necrosis and degree of vascularity present in different portions of the tumor. Tumor giant cells are frequently noted. In spite of the histologic evidence of malignancy, the solitary tumors tend to infiltrate locally and frequently do not metastasize until late. Thus, clinically, these localized tumors are of great importance because, if diagnosed early, they may be completely excised.

SUMMARY

Four cases of primary mesothelioma of the pleura are reported. Three of these tumors were of the solitary type, two of which were considered malignant. One malignant diffuse mesothelioma is included in this report.

SUMARIO

Mesotelioma Pleural: Presentación de Cuatro Casos

Preséntanse 4 casos de mesotelioma primario de la pleura. Tres de los tumores eran del tipo solitario, considerándose 2 de ellos como malignos. En la comunicación figura un mesotelioma maligno difuso.

RESUME

Mésothéliome pleural: Rapport sur quatre cas

Quatre cas de mésothéliome primaire de la plèvre sont rapportés. Trois des tumeurs appartenaient à la forme solitaire; deux d'entre elles étaient considérées malignes. Un cas de mésothéliome malin diffus est inclus dans ces observations.

Acknowledgments

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RUPTURE OF THE SPLEEN AS A SOURCE OF FATAL INTRAPERITONEAL HEMORRHAGE ASSOCIATED WITH PNEUMOPERITONEUM[1]

ROBERT K. OLIVER, FRANCIS M. THIGPEN, AND BRUCE F. HOLDING, JR.

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Intraperitoneal hemorrhage is a rare complication of pneumoperitoneum, but in 1949 Cornwall and Patridge (1) reported a case in which death resulted from puncture of a small vein in the greater omentum. Larkin and Phillips (2) reported a nonfatal intraperitoneal hemorrhage. In their case, although the abdomen was distended with blood, no bleeding point could be identified at laparotomy. Torsion of the spleen following pneumoperitoneum has been previously reported by Middleton, Pickett, and Singleton (3) and also two cases by Falor and Angus (4). In 1948, Trimble and associates (5) listed "hemorrhage in spleen" as a complication of pneumoperitoneum which occurred in one case, although no details were given. Also a death from oxygen injection in the spleen has been recorded (6). The following case represents a complication of pneumoperitoneum which the writers believe has not heretofore been reported.

CASE REPORT

The patient, a 29-year-old white male, was admitted to the Montgomery Tuberculosis Sanatorium on March 11, 1954, with pulmonary tuberculosis, classifiable as far advanced (C) (figure 1). The admission history and the physical and laboratory examinations revealed evidence of his pulmonary disease but were otherwise noncontributory except examination of the feces, which showed hookworm ova. Because of this finding, the patient was subsequently treated with tetrachlorethylene. On admission to the hospital, the patient was started on a regimen of bed rest, chemotherapy, and pneumoperitoneum.

The initial pneumoperitoneum was administered on March 22, 1954, the needle being inserted two inches inferiorly and laterally to the umbilicus in the left lower quadrant. The patient seemed to tolerate his refills well.

On June 25, three days following his most recent previous refill and three months after induction of the pneumoperitoneum, he complained of a moderately severe, sharp pain in the left upper abdomen which seemed to be accentuated slightly by deep breathing and coughing but was unaffected by position. The patient stated that he had experienced similar discomfort on two or three previous occasions following his pneumoperitoneum refills but the pain had always subsided spontaneously within a day or so. He denied nausea or vomiting and said that he had had a normal bowel movement that morning.

Examination revealed no remarkable physical findings except tympany of the entire abdomen, attributed to his pneumoperitoneum, and some slight left costovertebral angle tenderness. The temperature was 98.6°F., pulse 88 per minute, respiration 25 per minute, systolic blood pressure 120 and diastolic 80 in mm. of mercury. Urinalysis revealed no abnormalities.

The following day the patient was still complaining but stated that the pain was more intense and seemed to radiate laterally and posteriorly around the left inferior border of the costal margin to the mid-lumbar area. He complained of some nausea but no vomiting. The temperature now was 99°F., and urinalysis revealed only considerable amorphous precipitates; however, the total leukocyte count was 22,000 per cu. mm. Fluoroscopy revealed the spleen to be considerably enlarged, this finding being confirmed by an upright film of the abdomen (figure 2). The patient's pneumoperitoneum was aspirated, with

[1] From the Montgomery Tuberculosis Sanatorium, Montgomery, Alabama.

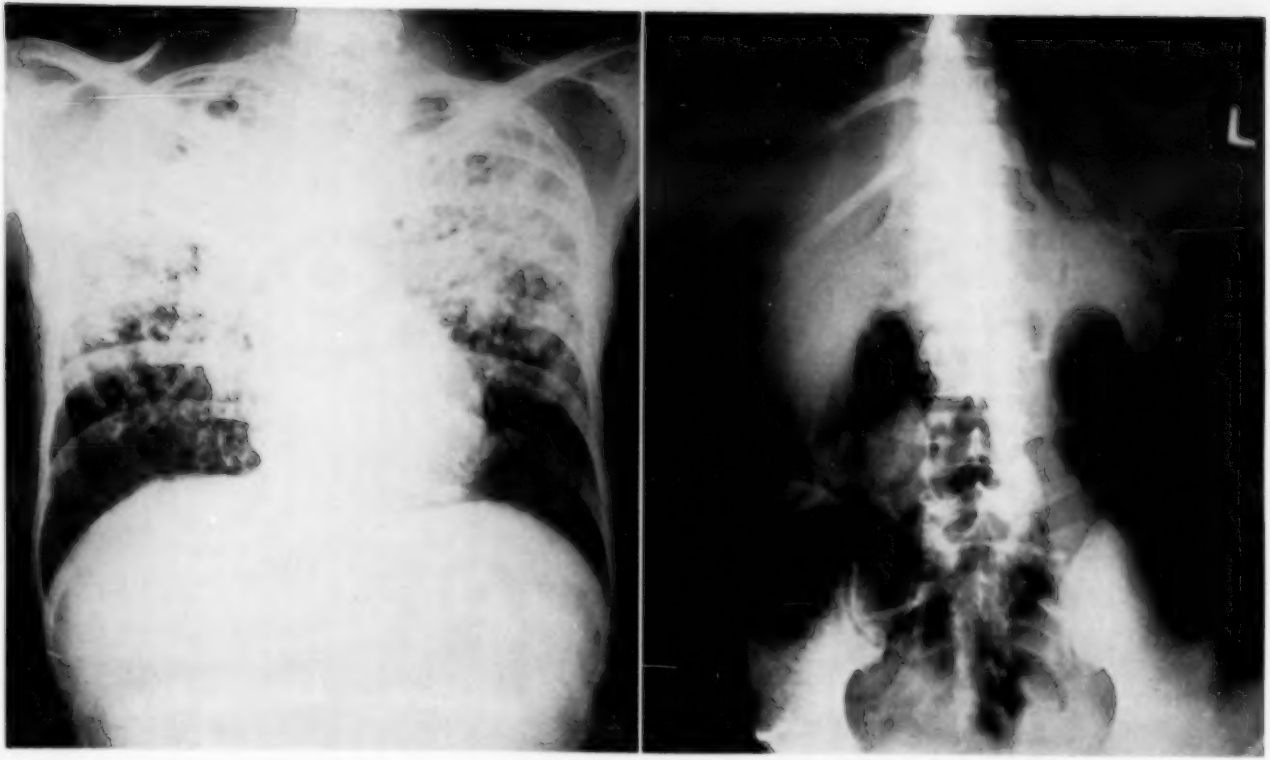

FIG. 1. (Left) Roentgenogram taken on March 11, 1954, on admission to the hospital, showing evidence of bilateral tuberculosis.
FIG. 2. (Right) Roentgenogram taken on June 26, 1954, one day before death, showing the enlarged spleen and pneumoperitoneum.

slightly more than 2,000 cc. of air removed by means of a Potter-Kirschner needle. He was then placed on strict bed rest in the Trendelenberg position in an effort to return the spleen to a more normal position. An ice pack was applied to the abdomen, and 50 mg. of meperidine hydrochloride were administered. Within one hour after the above measures were instituted, the patient showed dramatic relief and was complaining of only a slight abdominal discomfort. Physical examination at this time was not remarkable, and it was decided after surgical consultation that surgical intervention was not warranted. The patient continued to improve and tolerated a soft diet well, except that he vomited a glassful of water that was consumed immediately after receiving 50 mg. of meperidine hydrochloride at 9:00 p.m.

The morning of June 27 (third day after onset) found the patient feeling quite well and completely free of pain. After eating a complete breakfast, he was being shaved by the hospital barber when he complained of sudden dizziness. The nurse in charge responded immediately to the call bell and found the patient in a state of collapse. The medical director was notified and, within fifteen minutes following the patient's first complaint, massive intravenous therapy with blood plasma and glucose, oxygen inhalation by nasal catheter, and naso-gastric suction were undertaken.

Examination showed the patient to be in an extreme state of shock with the blood pressure unobtainable, pulse very rapid and thready, and the abdomen becoming increasingly distended. Preparations for an emergency laparotomy were instituted, and local blood banks were contacted in order to obtain whole blood. While the patient was being taken to the operating room, his respiratory movements ceased and, despite the use of positive pressure oxygen breathing, intravenous caffeine-sodium benzoate, and the intracardiac injection of epinephrine, the patient died.

Approximately twenty minutes after death, post-mortem examination revealed the entire abdominal cavity to be distended with a rather thin sanguineous fluid with large blood clots filling the lateral gutters. All of the abdominal viscera were within normal limits except the spleen, which appeared to be enlarged to several times its normal size with a 4 cm. rent in the posterolateral portion of the capsule and a 2 cm. laceration of the pedicle. Between the tail of the pancreas and the adjacent portion of the spleen some fibrous adhesions were noted. The pathologic report is as follows:

> Specimen consists of a spleen and a portion of the tail of the pancreas and a segment of fatty tissue apparently representing mesentery. The tail of the pancreas is densely adherent to the spleen and at the splenic tissue near the pedicle of the spleen. The surrounding tissue is hemorrhagic, the hemorrhage showing no evidence of organization. The spleen is greatly enlarged, weighing an estimated 600 gm. and measuring 17 by 10 by 4 cm. The surface is fairly smooth with only occasional nodules. The capsule of the spleen is not notably thickened, but at the lateral margin are several old yellowish infarcts. The splenic pulp is firm and beefy red and shows marked decrease in prominence of the malpighian corpuscles. Sections through the pancreas show apparently increased fibrous tissue and a peculiar waxy pallor of the substance.
>
> *Diagnosis:* Congestive splenomegaly.
>
> *Comment:* The adhesions of the tail of the pancreas to the spleen can probably be explained on the basis of several pneumoperitoneum refills. Thus, the shift in position caused the enormously enlarged spleen to exert considerable drag at the pedicle due to the fibrous adhesions to the relatively fixed pancreas. This in turn resulted in the laceration and a fatal hemorrhage.

COMMENT

It seems probable in this case that pneumoperitoneum, producing ptosis of the abdominal viscera, caused a torsion of the splenic pedicle with subsequent passive congestion producing the symptoms described above. However, no abnormalities of the splenic

pedicle or its ligamentous structures could be demonstrated which would confirm this impression. It is not at all clear why the splenic pedicle would suddenly rupture after relief of the congestion had apparently been obtained.

SUMMARY

A case of fatal hemorrhage caused by rupture of the splenic pedicle in association with pneumoperitoneum is reported. When torsion of the spleen is suspected, even in the absence of physical findings, it is suggested that laparotomy is indicated.

SUMARIO

La Rotura del Bazo como Causa de Hemorragia Intraperitoneal Letal Associada con el Neumoperitoneo

Preséntase un caso de hemorragia letal ocasionada por rotura del pedículo esplénico asociada con el neumoperitoneo. Siempre que se sospeche torsión del bazo, aun no habiendo hallazgos físicos, parece estar indicada la laparotomía.

RESUME

Rupture de la rate à l'origine d'une hémorragie intrapéritonéale en rapport avec un pneumopéritoine

Observation d'une hémorragie fatale déterminée par la rupture du pédicule splénique associée à un pneumpéritoine. Même en l'absence de signes physiques, quand il y a lieu d'envisager une torsion de la rate, l'auteur considère que la laparotomie est indiquée.

Acknowledgments

Grateful appreciation is expressed to Dr. R. C. Henry for his pathological interpretations and to Miss Emily Wooten and Mrs. Sibyl Day for their aid in the preparation of this manuscript.

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SPONTANEOUS PNEUMOTHORAX ON THE RIGHT SIDE FOLLOWING PNEUMOPERITONEUM[1]

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INTRODUCTION

Artificial pneumoperitoneum in the treatment of tuberculosis is not a new procedure. It was first introduced as a therapeutic measure by Vajda in Europe and Banyai in this country in the early nineteen thirties. Since that time its popularity has grown and its use has progressively increased during the past two decades. Although in the past it has been considered a relatively innocuous procedure, more and more cases of various complications following pneumoperitoneum are being published in the literature. An excellent review of these complications was published by Stein (1) in 1951.

One of the more unusual complications which may follow pneumoperitoneum is a right-sided pneumothorax. This may occur with or without loss of air from the pneumoperitoneum. Prior to the report of Ross and Farber (2), only five cases of pneumothorax complicating pneumoperitoneum with concomitant disappearance of the air intraperitoneally have been recorded. Ross and Farber observed three cases and added another twelve following a survey of the experience of a group of chest physicians in California. Additional reports have been published by Wu and Neptune (3) in 1951 and Vysniauskas and Brueckner (4) in 1953.

The present report, like those previously published, deals with a case of spontaneous pneumothorax on the right side with the simultaneous disappearance of the abdominal air. Unlike the cases reported by Guillaudeu and Stewart (5), the patient did not, at any time, show a diaphragmatic pneumocele.

The present case was considered worthy of a report because the postulated diaphragmatic defect was confirmed when the patient came to pulmonary resection.

CASE REPORT

M. B. M., a 29-year-old graduate nurse, was admitted to the West Tennessee Tuberculosis Hospital on July 20, 1953, because of a pulmonary lesion found on a public health service chest film dated June 26, 1953.

On admission, the patient stated that she was well and working as a private duty nurse until January, 1953, when she became ill with "bronchitis." Following this illness the patient noticed a generalized lassitude and some exertional dyspnea. On June 26, 1953, a public health service roentgenogram was taken, and a diagnosis of pulmonary tuberculosis, chronic, moderately advanced, active, was made. Hospitalization was advised.

The roentgenogram obtained on admission to the hospital on July 20, 1953 (figure 1), revealed a mixed type of infiltrate extending from the right apex down to the third anterior rib and a definite 1 cm. cavity at the level of the third anterior rib. The patient was started on chemotherapy consisting of 1 gm. of streptomycin twice weekly and 9 gm. of para-aminosalicylic acid (PAS) daily.

On July 23, 1953, an initial pneumoperitoneum was induced. Eight hundred cubic centimeters of air were introduced approximately two inches to the left of the umbilicus. Final pressures were plus 3, plus 5. That afternoon fluoroscopic examination revealed air beneath the left dome of the diaphragm. A refill of 1,000 cc. was given the next day, July

[1] From the West Tennessee Tuberculosis Hospital, Memphis, Tennessee.

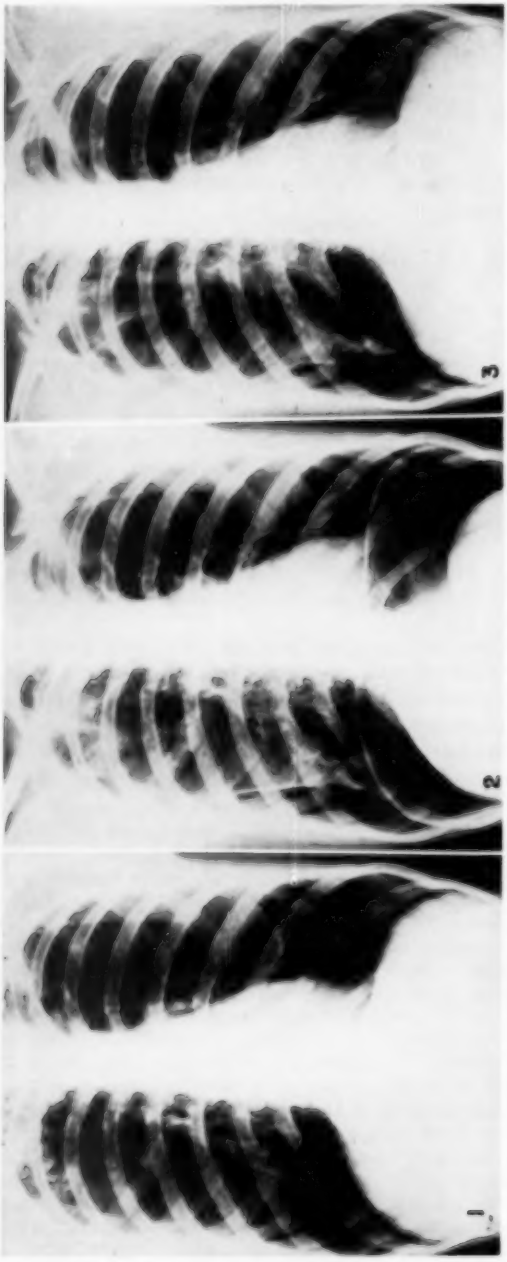

FIG. 1. July 29, 1953. Tuberculous infiltrate extending from right apex to second anterior interspace.

FIG. 2. July 27, 1953. Pneumoperitoneum with spontaneous pneumothorax on the right side.

FIG. 3. July 30, 1953. Complete disappearance of pneumoperitoneum. Spontaneous pneumothorax on the right still present.

24, 1953, and then fluoroscopic examination following the refill revealed air beneath both domes of the diaphragm.

On the morning of July 25, 1953, prior to giving a refill, fluoroscopic examination revealed a partial pneumothorax on the right extending from the mid-thorax down to the base. The upper half of the right lung was held up by massive adhesions. There was no pain or dyspnea. No refill was given that day. Two days later, July 27, 1953 (figure 2), there was seen less air in the abdomen with slightly more collapse of the right base. A small refill was given intra-abdominally, with final pressures reaching plus 3, plus 5. Chest roentgenograms revealed collapse of the right lung base and decrease of the air in the peritoneum. Another roentgenogram on July 30, 1953 (figure 3), revealed complete disappearance of the pneumoperitoneum.

No more air refills were given and on July 31, 1953, 750 cc. of air were aspirated from the right chest. A roentgenogram on August 4, 1953, revealed a complete disappearance of the pneumoperitoneum with almost complete re-expansion of the pneumothorax on the right. On August 6, 1953, a right phrenic crush was done and the patient was continued on bed rest and chemotherapy.

On February 4, 1954, resection of the apical and posterior segments of the right upper lobe was done. Examination of the diaphragm revealed a defect in the outer crus, with absence of muscular attachments to the lateral chest wall. The space, usually occupied by muscle, was filled with connective tissue. Because of the lack of any herniation into the thorax, no surgical repair of the defect was done. The postoperative convalescence was essentially uneventful.

COMMENT

The exact mechanism of loss of abdominal air in cases of spontaneous pneumothorax following therapeutic pneumoperitoneum is still unknown. One theory advocated by Banyai and Jurgens (6) is that the air follows along the connective tissue sheath of the esophagus and great vessels through the diaphragmatic hiatus into the mediastinum. As a result of increased tension within the mediastinum, rupture of the pleural membrane occurs with the production of a pneumothorax. Against this theory is the fact that spontaneous pneumothorax associated with mediastinal emphysema is usually on the left side.

A second theory is based on the presence of a diaphragmatic defect which allows free passage of air between peritoneal and pleural cavities. Meyer (7) has pointed out that there are three weak points in the diaphragm which are the most common sites of diaphragmatic hernias and, therefore, may be a source of direct communication between the peritoneal and pleural cavities:

1. Foramen of Bochdalek, which is a pleuroperitoneal hiatus, situated dorsolaterally. The apex is curved toward the central tendon upward and forward and the base is turned downward and backward and partially rests on the twelfth rib.
2. Outer crus. There may be a triangular space which separates the muscle fibers of the outer crura of the lumbar portion and the last muscular portion of the costal portion of the diaphragm. This space is filled by connective tissue and covered by the pleura above and by the peritoneum below. The liver plays a protective role on the right, and hernias through this opening occur mostly on the left. With displacement of the liver following pneumoperitoneum, this protection is removed and formation of right hernia and shunt can occur.
3. Foramina of Morgagni or Larrey's spaces on both sides of the xiphoid process due to the developmental failures of fusion.

Meyer does not believe that the foramina of the aorta, vena cava, esophagus, splanchnic nerves, and azygos veins are sites for hernia.

The present case would appear to fall into the second category outlined by Meyer. It differs from the majority of cases reported in which pneumothorax occurred months or years after pneumoperitoneum treatment. Instead, the present case resembles those cases reported by Wu and Neptune and Vysniauskas and Brueckner in which pneumothorax immediately followed administration of initial pneumoperitoneum. The present case is unique in that it is one of the few cases in which the presence of a diaphragmatic defect was confirmed by operation.

SUMMARY

Right-sided pneumothorax following pneumoperitoneum is not an uncommon occurrence. The majority of cases associated with loss of intra-abdominal air occur on the right side. Congenital diaphragmatic defects and displacement of the liver by pneumoperitoneum appear to be the underlying causes. A report of a case of spontaneous pneumothorax following pneumoperitoneum secondary to congenital diaphragmatic defects confirmed by surgical exploration is presented.

SUMARIO

Neumotórax Espontáneo del Lado Derecho Consecutivo al Neumoperitoneo

El neumotórax dextrolateral consecutivo al neumoperitoneo no es acontecimiento raro. La mayoría de los casos vinculados con pérdida de aire intraabdominal corresponden al lado derecho, pareciendo ser las causas subyacentes vicios congénitos del diafragma y desplazamiento del hígado por el neumoperitoneo. Preséntase la descripción de un caso de neumotórax espontáneo consecutivo al neumoperitoneo y secundario a defectos congénitos del diafragma, confirmado por la exploración quirúrgica.

RESUME

Pneumothorax spontané du coté droit succédant au pneumopéritoine

Le pneumothorax droit à la suite de la création d'un pneumopéritoine n'est pas une rareté. La majorité des cas où se produit une fuite de l'air intra-abdominal se manifestent du côté droit. Les anomalies congénitales du diaphragme et le déplacement du foie sous l'influence du pneumopéritoine paraissent à la base de cet accident. L'auteur rapporte un cas de pneumothorax spontané, après instauration d'un pneumopéritoine, qui était dû à des anomalies congénitales du diaphragme confirmées par l'exploration chirurgicale.

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Editorial

Emotional Problems in the Treatment of Tuberculosis

The fact that 35 to 50 per cent of patients with tuberculosis do not complete the residential treatment of their disease is one striking bit of evidence that something is awry with our handling of these patients. In a broad sense the reasons for these failures are the emotional problems of the patient which are not properly handled. Our handling of the disease tuberculosis is tremendously improved but, if our handling of the diseased people is poor, they do not and cannot cooperate in the treatment. Not only are the advantages of our improved therapy lost, but these patients return to their communities and become sources of infection.

What has a psychiatrist to offer in this situation? There are two main contributions psychiatry can make—first, a general attitude toward people and the role anxiety plays in shaping their behavior; and, second, some techniques for finding out our patients' concerns so that they can be relieved.

The presentation to a person of the diagnosis of tuberculosis is inevitably an anxiety-producing situation for the patient. It may also be anxiety-producing for the physician or other worker in the field of tuberculosis who has to impart the bad news. The physician knows about tuberculosis and the parts of the situation which would be anxiety-producing to him if he found he had the disease. Therefore, in a conscious endeavor to relieve the patient's anxiety (but probably really to relieve his own), he is apt to launch into an attempt to reassure the patient about those things which would have made him anxious. This is futile, if not pernicious, as the patient's knowledge of tuberculosis is different from ours, his personality is different, his personal problems are different. The anxiety the diagnosis produces in him is distinct and unique to him. We must assume that it produces these anxieties in him, and then induce him to talk about his own anxieties about which we can reassure him. To do this, we must remain silent at first. This increases the patient's anxiety to the point where he may talk and ask us questions. If he does not do so—after a few minutes of silence we may ask—what does this mean to you, or, how do you feel about this. This encourages him to talk. We avoid rushing in with reassurance until we feel we have brought out the major part of his concerns. If we reassure quickly, we reassure only about the minor concerns and cut off discussion of the more major ones because they are usually brought out last.

We must be careful in our reassurance not to go beyond our own certain knowledge. With the rapid changes in tuberculosis therapy, we are not certain of the length and method of treatment; and we must not give the patient certainty when we have none. Setting of dates and specific duration of treatment is especially to be avoided, as a minimum time becomes a maximum for our patient and, if this is not fulfilled, it undermines his confidence in all the tuberculosis treatment team and results in diminished cooperation if not flight from therapy. The patient can be reassured that treatment has greatly improved and that he will be treated until he is well, although we cannot be certain of the exact time.

In the sanatorium certain things are expected of the patient, although we may never have analyzed just what these are from an emotional point of view. The patient is asked to give up his possibly hard-earned maturity. He is asked (though not in these terms) to regress to the status of a child. No longer is he to be the active, independent, giving parent or adult. He is to become passive, dependent, and receptive. He is to lie quietly, let others do most things for him, and to do little or nothing for others in return. This is a tremendous change in his way of living, and the ease with which the patient makes this change depends upon his past history of dependency and maturity, his personality structure, and his habitual techniques of relieving the anxiety which we are all prey to.

To some people, this giving up of maturity and relaxing into a dependent security is regarded as a blessing. They have maintained or achieved their maturity with difficulty—or not at all—and it is a great relief to have nothing expected of them. These patients may appear to be "good" patients in the sanatorium, but the difficulties in rehabilitation are obvious. These patients may encounter difficulty in the sanatorium, however, on account of their complete regression. As children, they cried and demanded what they wanted. Their continual dependent demanding may get under the skin of the personnel who work with them, possibly because we, too, at times would like to be waited on and resent their getting what we want and can't have. This leads to the rejection by the staff—so, at the same instant, we demand regression to a childhood level and we also find fault with the patient for doing so. Another type of patient has grown up despite his parents who tried to keep him immature and dependent on them. He has had to go through quite a rebellion at adolescence. Here are we in a sanatorium playing the parental role all over again to which the patient is so apt to react with his pattern of adolescence revolt, which leads to breaking of regulations or, if the situation is repressively handled, flight from the hospital. Another type of person has relieved his anxieties by action. Whenever he has been upset, he has thrown himself into activities to take his mind off his troubles. In a tuberculosis sanatorium, his anxieties are greatly increased by the fears relating to his disease, his concern about his family situation, and his economic helplessness. At the same time, his usual defense of activity is taken away. Psychiatrists believe that we all avoid anxiety almost at any cost. We tend to think of the dangers of tuberculosis as being an adequate stimulus to treatment cooperation but, if the anxiety produced by the whole life situation of the patient under treatment is greater than that which he has about his disease, he may break off the treatment as it creates an intolerable anxiety.

Some patients run into difficulty over the deprivation in the sexual sphere produced by the treatment situation. To some, it is a matter of relief of physical tension. These tensions, if not relieved, give rise to anxiety, emotional tensions, and physical restlessness which is inimical to rest. It may produce a sexual fantasy life repugnant to the patient's moral standards and, thus, quite disturbing; or, in fact, it may lead to extramarital relationship, which may prove most upsetting and guilt-producing, to escape from which the patient may leave treatment. Possibly more important than the physical tensions of sexual deprivation is the emotional loss. To many people, their sexual activity is the proof to

them that they are fully loved by someone, and this loss of feeling of being loved may prove intolerable. To some people, the sexual sphere is the only one where they are successful, and to lose this only source of self-esteem produces too much emotional disturbance to be tolerated.

In all the types cited above—and there are many more—understanding of patients' individual emotional problems and the flexible adaptation of treatment to them is necessary if the patient is to have optimal rest or, in many cases, to complete his treatment.

The rehabilitation of patients after treatment is another area in which emotional factors are predominant. Here, in essence, we try to undo the regressed, immature, passive, receptive, and dependent role we have asked the patient to assume and ask him to become mature, independent, and productive again. Some of these difficulties can be alleviated by allowing the patient to maintain some degree of maturity during the treatment process. By presenting him with different alternatives in planning his treatment, the support of his family, et cetera, we may nurture his self-esteem and the feeling that he is capable of directing his own affairs. The amount of problem left at the time of rehabilitation depends upon many factors in the personality of the patient, his degree of maturity before becoming ill, the degree of regression in the hospital, his methods of handling anxiety, the amount of tension and acceptance at home, residual symptoms, and the fears of recurrence (often overstressed by the doctors, producing a chronic invalid). Thus, in the diagnosis, the treatment, and the rehabilitation of people suffering from tuberculosis, emotional factors are of paramount importance. These factors are unique for each individual and there can be no easy rules of thumb. We must have techniques to find out our patients' problems and the flexibility to meet these problems once discovered. The major technique psychiatrists have to offer those responsible for tuberculous patients is simple in words—Get the patient to talk about himself. Most people enjoy the opportunity but at the same time may have a tendency to avoid the significantly disturbing areas. We, on our part, must learn to listen quietly, sympathetically, and never by word, sigh, or gesture express condemnation of the patient. If we do, he just won't talk to us. He may tell us things which are unacceptable to our moral standards. It is not our job to re-make his character but to treat his tuberculosis. Patients may talk a little and then stop. We feel certain there is more to say. Here a nudging technique is needed; a simple "and then" may start him off again. Or you may repeat his last phrase—"So you worry about your job" and stimulate him to proceed. Or we may ask, "How do you feel about that?" In all of these, it is to be noted that we have introduced none of our ideas but just given the opportunity to the patient to talk. These techniques are equally applicable to case finding, medical management, and rehabilitation workers.

The goal is a patient who understands his disease, can accept a treatment which does not violate his personality, and who can return to the community as a mature, responsible, productive adult.

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Notes

RELAPSE RATES AFTER CHEMOTHERAPY IN CHRONIC FIBROCASEOUS PULMONARY TUBERCULOSIS

Clinical trials with isoniazid in the treatment of pulmonary tuberculosis have been in progress at Guy's Hospital since 1952. The earlier results have been reported previously[1, 2] and from them it was concluded that a regimen of isoniazid and streptomycin together was very effective in controlling chronic fibrocaseous disease. Further trials, using various regimens of administration, including the use of para-aminosalicylic acid (PAS), have been made since then, and "sputum relapse" rates for six months following the end of treatment have been studied. The small number of cases on each regimen does not allow a comparison to be made between them. Nevertheless, the over-all percentage of patients in whose sputum tubercle bacilli reappeared in the months following a successful course of treatment was so high that it was considered appropriate that it be recorded.

Forty-seven patients with chronic pulmonary tuberculosis, with tubercle bacilli in the sputum, have been treated as outpatients. They correspond to those in Group III of the British Medical Research Council 1952[3] report. Four treatment regimens (*B*, *C*, *E*, and *F*) have been studied. They consisted of various combinations of isoniazid and PAS administered orally and streptomycin intramuscularly. In detail they are as follows:

Regimen B: Isoniazid, 250 mg. daily, and streptomycin, 1 gm. six times each week, for eighteen weeks

Regimen C: Isoniazid, 250 mg. daily, and streptomycin, 1 gm. twice weekly, for twenty-four weeks

Regimen E: Rotating therapy (twenty-four weeks):

First to fourth week—streptomycin, 1 gm. twice weekly, and isoniazid, 250 mg. daily

Fifth to eighth week—PAS, 10 gm. daily, and isoniazid, 250 mg. daily

Ninth to twelfth week—PAS, 10 gm. daily, and streptomycin, 1 gm. twice weekly

Thirteenth to twenty-fourth week—above cycle repeated

Regimen F: Isoniazid, 250 mg., and PAS, 10 gm. daily, with streptomycin, 1 gm. twice weekly for twenty-four weeks

With all of these combinations the patients improved steadily and, once tubercle bacilli disappeared from the sputum, no bacteriologic relapse was seen during treatment.

After treatment ended, it was soon judged clinically that many patients were not doing well. Cough, sputum, and fatigue reappeared. Individual and group weights began to fall and the erythrocyte sedimentation rates began to rise. Most striking, however, was the increasing number of patients who once again were discharging tubercle bacilli in the sputum (table 1).

Of the 47 patients who started treatment, 3 did not complete their scheduled courses: one had to be withdrawn as he became sensitive to streptomycin; one died of bronchopneumonia during the third month; and the third patient defaulted. Thirty of the remaining 44 patients were found to have sputum negative for tubercle bacilli when

[1] Joiner, C. L., *et al.*: Lancet, 1952, *2*, 843.

[2] Joiner, C. L., *et al.*: Lancet, 1953, *2*, 152.

[3] Medical Research Council: Brit. M. J., 1952, *2*, 735.

TABLE 1

NUMBERS OF PATIENTS WITH SPUTUM NEGATIVE FOR TUBERCLE BACILLI AFTER VARIOUS REGIMENS OF TREATMENT (*B*, *C*, *E*, *F*) IN THE LAST MONTH (0) AND THE SUBSEQUENT SIX MONTHS (1–6)

	Number of Patients	0	1	2	3	4	5	6
Regimen *B*	11	6/11	5/11	5/11	5/11	2/11	1/11	0/11
Regimen *C*	9	7/8	6/8	5/8	4/7	3/7	3/7	3/7
Regimen *E*	13	7/12	4/10	4/10	3/10	3/10	2/10	2/10
Regimen *F*	14	10/13	5/11	5/11	5/11	2/11	1/11	1/11
Total	47	30/44	20/40	19/40	17/39	10/39	7/39	6/39
Per cent		(68)	(50)	(47)	(44)	(25)	(18)	(15)

Numerators indicate number remaining "sputum-negative"; denominators, the total number left in the group. Details of regimens *B*, *C*, *E*, *F* in text.

TABLE 2

NUMBERS OF PATIENTS (WHO COMPLETED TREATMENT AND FOLLOW-UP) WHO WERE "SPUTUM-NEGATIVE" IN THE LAST MONTH OF TREATMENT (0) AND THOSE WHO REMAINED "NEGATIVE" DURING THE SUBSEQUENT SIX MONTHS (1–6)

Month	0	1	2	3	4	5	6
Number negative	25	19	18	17	10	7	6
Per cent	100	76	72	68	40	28	24

treatment was completed. The criteria used for the designation "sputum conversion" have been defined elsewhere[1]. Briefly, no patient was reported to have "negative sputum" unless no tubercle bacilli had been found in any of the six specimens examined microscopically during the previous month. All slides reported as negative were checked by a second observer. While it is agreed that this criterion of negativity was not as strict as if cultures had been performed, it has been found, nevertheless, to be an extremely satisfactory method by which to assess the progress of the chronic type of case with which this trial is concerned.

It will be seen from table 1 that 5 patients who finished their course of treatment did not complete the follow-up period. Four of these, none of whom had tubercle bacilli in the sputum, left the trial within a month of the end of treatment for the following reasons: 2 patients were considered suitable for surgical procedures, one patient defaulted, and one patient took his own life. The fifth patient died of bronchopneumonia in the third month of the follow-up period. He was still "sputum-negative" at the time of his death.

As these losses occurred in the initial stages of the period under review, they were excluded from the series.

Thus, 25 patients with sputum negative for tubercle bacilli at the end of treatment completed the follow-up period. In table 2 are shown the number of those who continued to have sputum negative for tubercle bacilli at monthly intervals throughout the six months' follow-up period.

In some instances, patients whose sputum again became positive for tubercle bacilli

[1] COLLARD, P., *et al.*: Lancet, 1953, *2*, 155.

were re-treated before the end of the six-month period, as it was not believed justifiable to delay further therapy in severely ill cases. For the purposes of follow-up studies, they were regarded as having had "bacteriologic relapse" from the time of their first "positive sputum" examination.

* * *

With the number of cases under review, no comparison can be made of the efficacy of each of the four regimens described above. The essential pattern was similar in each. Patients did extremely well while on treatment, and a surprisingly large "sputum conversion" rate was achieved, considering the advanced type of chronic fibrocaseous disease present. Furthermore, the patients were treated as outpatients and were not confined to bed, their regimens varying from sitting at home to a full-time sedentary occupation.

In the six months after treatment had ended, however, the great majority showed various degrees of clinical deterioration, accompanied by the return of tubercle bacilli in the sputum.

It is therefore concluded that the duration of treatment (eighteen to twenty-four weeks) was too short. It might be that more permanent benefit would have followed had therapy been continued for a substantially longer period; indeed, it may prove necessary to treat this type of patient indefinitely.

Patients who continued to discharge tubercle bacilli in the sputum during their initial course of chemotherapy and those who relapsed bacteriologically in the follow-up period are now being re-treated on regimen *C* or *E*. The results will be published at a later date but, after periods ranging from four to six months, they are comparable with those obtained initially, the majority of the patients again showing great clinical and bacteriologic improvement. Isoniazid-streptomycin, with or without the addition of PAS, seems to offer the best therapeutic answer to the problem of chronic pulmonary tuberculosis in the present state of our knowledge, and it would appear that courses of treatment should be prolonged beyond six months.

In summary: The "bacteriologic relapse" rates on follow-up of 39 patients who had been treated with various chemotherapeutic regimens for eighteen to twenty-four weeks are reported. At the end of treatment, 30 patients had become "sputum-negative." Within six months, 24 of these patients had experienced "bacteriologic relapse," as judged by microscopic examination of the sputum. It is concluded that courses of antituberculous chemotherapy should exceed six months if early "bacteriologic relapse" is to be prevented.

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A COLORIMETRIC TEST FOR MEASURING CATALASE ACTIVITY OF CULTURES OF M. TUBERCULOSIS

It has long been established that catalase is produced by actively growing cultures of *M. tuberculosis*, as well as by many other bacteria. Recently it was shown[1] that the iron-porphyrin in catalase reacts with isoniazid under certain physiologic conditions, thus inactivating the catalytic ability of the enzyme to decompose hydrogen-peroxide (H_2O_2) into water and oxygen. It was also demonstrated[1] that isoniazid-susceptible cultures of *M. tuberculosis* were catalase-active and that cultures of resistant tubercle bacilli were less active catalase producers or entirely lacked this capacity, depending upon the degree of resistance.

This report describes a colorimetric procedure for measuring the amount of catalase activity of cultures of *M. tuberculosis*.

After testing various procedures for measuring the presence of small amounts of H_2O_2 in solution, it was decided that the citric-acid–ammonium molybdate method[2] was the most useful. In order to apply this method, it was necessary to make the following determinations: total volume of the test, amount of culture to be used, amount of H_2O_2 needed, amount of citric acid and ammonium molybdate necessary, and an optimum incubation temperature and time period which would be conveniently workable.

Using one-fiftieth of the original amounts of citric acid and ammonium molybdate employed by Isaacs,[2] small amounts of H_2O_2 diluted with phosphate buffer pH7 were tested for color formation. It was found that, when 0.2 ml. of 6 per cent citric acid and 0.2 ml. of 1.1 per cent ammonium molybdate were added to 0.4 ml. of phosphate buffer pH7 and 0.2 ml. of 0.3 per cent H_2O_2 (0.0006 gm.), a clear yellow color appeared immediately which was deep enough for further dilutions proportional to correspondingly smaller amounts of H_2O_2 diluted in phosphate buffer.

A permanent color standard was then prepared by dissolving 0.4 gm. of potassium chromate (U.S.P.) in a liter of distilled water. It was seen that 1 ml. of the above-mentioned yellow 0.04 per cent solution of chromate, in a 0.5- by 4-inch test tube, matched exactly the intensity of the yellow color which appeared when 0.2 ml. of 0.3 per cent H_2O_2 (0.0006 gm.) in 0.4 ml. of phosphate buffer pH7 and 0.2 ml. of 6 per cent citric acid and 0.2 ml. of 1.1 per cent of ammonium molybdate were mixed together in a 0.5- by 4-inch matched test tube. Therefore this concentration of potassium chromate (of the same yellow color intensity as the tube containing 0.2 ml. of 0.3 per cent H_2O_2 (0.0006 gm.)) was considered the 100 per cent H_2O_2 standard. Other dilutions of chromate were then prepared in decreasing amounts to correspond to 50 per cent (0.0003 gm. per ml.), 25 per cent (0.00015 gm. per ml.), 10 per cent (0.00006 gm. per ml.) and 1 per cent (0.000006 gm. per ml.). The absence of H_2O_2 was represented by 1 ml. of colorless phosphate buffer. The permanent standard color tubes were then sealed to prevent evaporation.

In order to determine the amount of culture to be used in the test, as well as the incubation temperature and time, ten-day-old transplants of 50 cultures of *M. tuberculosis* susceptible to 0.1 γ of isoniazid per ml. of medium and 50 cultures of tubercle bacilli resistant to isoniazid, which were grown for many generations on 100 γ of isoniazid per ml. of medium, were used. By varying the amounts of culture, it was determined that 2 loopfuls (3 mm. diameter of 19-gauge wire) of isoniazid-susceptible, young, actively grow-

[1] Middlebrook, G.: Am. Rev. Tubere., 1954, *69*, 471.

[2] Isaacs, M. L.: J. Am. Chem. Soc., 1922, *44?*, 162.

ing colonies of *M. tuberculosis* (ten-day-old transplants of stock cultures and three-week-old primary growths) contained a sufficient amount of catalase to decompose completely 0.2 ml. of 0.3 per cent H_2O_2 (0.0006 gm.) to water and oxygen. Old cultures of tubercle bacilli do not produce clearly defined results and should not be used. Cultures for the catalase test should be young and actively growing on suitable media.

The incubation temperature of 6°C. (refrigerator temperature) was decided upon to ensure a convenient rate of catalase activity. Room temperature or higher, water bath temperatures up to 50°C., produced too rapid a rate of activity for accurate readings. The time required for completion of the test was determined by testing the 50 isoniazid-susceptible and 50 -resistant cultures of tubercle bacilli for catalase activity at 6°C. at varying time periods until all the H_2O_2 was decomposed in all the tests containing isoniazid-susceptible cultures. The optimum time required, namely, sixty minutes, was then determined.

The test procedure was then set up as follows: to 2 loopfuls (3 mm. diameter) of culture of young actively growing tubercle bacilli, grossly suspended in 0.4 ml. of phosphate buffer pH7 in a 0.5- by 4-inch test tube, was added 0.2 ml. of 0.3 per cent H_2O_2. The culture H_2O_2 mixture was incubated in the refrigerator at 6°C. for sixty minutes. Two-tenths of a milliliter each of 6 per cent citric acid and 1.1 per cent of ammonium molybdate were added in the given order.

Reading of results and comparisons with the color standards were made after the bacterial cells settled to the bottom of each tube (approximately thirty minutes), leaving a

TABLE 1

COMPARISON OF COLORIMETRIC CATALASE ACTIVITY TEST WITH TEST TUBE ISONIAZID-SUSCEPTIBILITY READINGS*

Number of Known Control Cultures	Number of Cultures	Amount of Growth on Isoniazid Medium				Amount of Remaining H_2O_2 After Incubation with Suspensions of Tubercle Bacilli				
		Control 0	0.1γ/Ml.	1.0γ/Ml.	5.0γ/Ml.	100 cu. mm.	50 cu. mm.	25 cu. mm.	10 cu. mm.	0
	79	1+ to 4+	0	0	0					79
	18	2+ to 4+	2+ to 4+	2+ to 4+	2+ to 4+	18				
	10	4+	4+	3+	1+ to 2+		10			
	2	3+	3+	2+	1+		2			
	5	2+	2+	1+ to 2+	1+		5			
	4	1+	1+	1+	1+		4			
	4	4+	4+	1+	1+			4		
	6	2+	2+	1+	1+			6		
	3	1+	1+	1+	Few colonies			3		
	5	4+	4+	1+	Few colonies				5	
	2	3+	3+	1+	0				2	
	4	2+	2+	1+	0 to few colonies				4	
	1	4+	4+	4+	4+		1			
	1	4+	4+	0	0		1			
	3	4+	4+	1+	0		2	1		
	1	4+	4+	4+	4+			1		
	2	4+	4+	4+	3+		1	1		
Susceptible (15)		4+	0	0	0					15
Resistant (15)		4+	4+	4+	4+	15				

* Drug-susceptibility tests were carried out by emulsifying the entire growth of the primary cultures and by inoculating 0.1 ml. of the suspension on each slant of drug medium as well as on the control slants.

clear yellow colored or colorless supernatant. Controls consisting of ten-day-old transplants of known isoniazid-susceptible and known-resistant cultures of *M. tuberculosis* were included. Results were recorded as 100 per cent, 50 per cent, et cetera, catalase activity as compared with the standards.

* * *

Employing the above tests, 150 young, actively growing primary cultures of tubercle bacilli growing on Löwenstein-Jensen or Peizer-Schechter media, from known tuberculous patients before and during isoniazid treatment, were tested.

All of the 50 isoniazid-susceptible cultures of tubercle bacilli showed positive catalase activity by completely decomposing the H_2O_2 in forty-five to sixty minutes at 6°C. This was indicated by a colorless result on addition of citric acid and ammonium molybdate. The 50 cultures of *M. tuberculosis*, grown for many generations on medium containing 100 γ of isoniazid per ml., showed no catalase activity. This was indicated by the appearance in these tests of a yellow color equivalent in intensity to the 100 per cent colorimeter tube (representing 0.0006 gm. or 0.2 ml. of 0.3 per cent of H_2O_2).

The 150 young, primary cultures of *M. tuberculosis* showed various ranges of catalase activity, from 0 to 100 per cent. This was indicated by the formation in the tubes of various intensities of yellow or lack of yellow. The results are seen in table 1. It may also be seen in the table that in this series there was fairly good agreement between the catalase-activity tests and the isoniazid tube drug-susceptibility tests of primary cultures of tubercle bacilli. Studies in progress in this laboratory seem to indicate that this test might be useful as a substitute for routine cultural drug-susceptibility tests and guinea pig virulence inoculations of tubercle bacilli from specimens of isoniazid-treated patients. These experiments, however, are not yet completed.

In summary: A colorimetric test, depending upon the action of hydrogen-peroxide on a molybdate in acid solution, was described for the purpose of determining the rate of catalase activity of tubercle bacilli in primary cultures from patients during isoniazid therapy. It was suggested that the colorimetric catalase test might be useful as a substitute for routine drug-susceptibility and guinea pig virulence tests after further studies are completed.

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INFLUENCE OF QUARTZ ON THE RECOVERABILITY OF TUBERCLE BACILLI FROM RESECTED PULMONARY LESIONS[1]

The original observation[2] that tubercle bacilli cannot be recovered by culture or animal inoculation from many lesions removed from patients who had received prolonged antituberculous drug therapy has now been amply confirmed. Many of these lesions contain intact acid-fast bacilli, at times in very large numbers, which are demonstrable in stained smear preparations. Naturally, inability to recover organisms from these lesions offers a challenge to the classical methods used in demonstrating the viability of tubercle bacilli from such pathologic material. Several attempts to meet this challenge have already been made, including: (*1*) washing the specimen to free it of residual drug; (*2*) planting the material on drug-containing media to detect drug-dependent organisms; (*3*) lowering resistance to infection of the test animals into which the material is inoculated by the administration of cortisone (guinea pigs) or the combination of cortisone plus irradiation with X-rays (mice)[3]; (*4*) incubating the cultures in atmospheres containing different concentrations of oxygen and carbon dioxide.[4]

All of these methods have failed to increase the number of positive recoveries. Recently, Bernstein and Steenken[5] observed that the treatment of an aliquot of the homogenized specimen with bovine albumin prior to culture or animal inoculation failed to produce superior results over the ordinary method of suspending the homogenized material in physiologic saline.

Another study, in which the specimens were homogenized and washed with bovine albumin and incubation of the cultures was prolonged for many months, has been reported by Hobby and associates[6, 7], who obtained a higher percentage of positive recoveries than most other workers.

As early as 1922, Gye and Kettle[8] showed that most types of mycobacteria grow with unusual rapidity in freshly formed silicotic lesions, especially those with necrosis. These investigators proved that human-type tubercle bacilli would proliferate without restraint in a silica abscess produced by injecting fine quartz beneath the skin of a white mouse. Gardner[9] observed that the Rl, a living attenuated strain of *Mycobacterium tuberculosis*

[1] This study was aided by grants from the Division of Research Grants and Fellowships of the National Institutes of Health, Public Health Service.

[2] D'Esopo, N., Bernstein, S., Lee, W. F., Decker, A. M., and Steenken, W., Jr.: Tr. Eleventh Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, Navy, St. Louis, Missouri, January, 1952, p. 230.

[3] Hall, W. H., and Gleason, D. F.: Tr. Twelfth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, Navy, Atlanta, Georgia, February, 1953, p. 219.

[4] San Fernando Veterans Administration Hospital: Study on the Chemotherapy of Tuberculosis, Quarterly Progress Report of the Veterans Administration, Army, Navy, April, 1954, p. 65.

[5] Bernstein, S., and Steenken, W., Jr.: Am. Rev. Tuberc., 1954, *70*, 370.

[6] Hobby, G. L., Auerbach, O., Lenert, T. F., Small, M. J., and Comer, J.: Tr. Thirteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, Navy, St. Louis, Missouri, February, 1954, p. 291.

[7] Hobby, G. L., Auerbach, O., Lenert, T. F., Small, M. J., and Comer, J. V.: Am. Rev. Tuberc., 1954, *70*, 191.

[8] Gye, W. E., and Kettle, E. H.: Brit. J. Exper. Path., 1922, *3*, 241.

[9] Gardner, L. U.: Tubercle, 1932, *13*, 504.

(orRlRv, its designation[10, 11] today) generally manifested a low but surprisingly constant degree of virulence for normal guinea pigs; but, when the animals had been subjected to the long-continued inhalation of pure quartz dust, an Rl inhalation infection was rendered progressive and often fatal.

These observations suggested to the Saranac Laboratory investigators[12] as well as to the present writers that the use of quartz might provide a method for the recovery of tubercle bacilli from resected pulmonary lesions when all other methods already tried had failed. The results of the studies conducted along this line at the Trudeau Laboratory will be presented in this communication. Preliminary reports of this study and another similar one have been presented elsewhere ([13, 14].

Preparation of 10 per cent aqueous suspension of quartz: Ten grams of dried quartz powder consisting of particles 1 to 3 microns in diameter, especially prepared by the Saranac Laboratory, were suspended in 100 ml. of distilled water in the following manner: The weighed dried quartz powder was placed on a large watch glass. Small amounts of water were added drop by drop and the powder was gradually brought into an even suspension with the aid of a rubber policeman. The suspension was then transferred to a 100 ml. volumetric flask, and water was added to the 100 ml. mark. This suspension was sterilized by autoclaving at 20 pounds of pressure for fifteen minutes.

As soon as possible after arrival in the laboratory, the resected lung specimens were examined by inspection and palpation and, using aseptic technique, the lesions were incised and enucleated from the surrounding tissue. The gross morphology was recorded. Direct smears were made of the contents and bacilli counts were recorded after staining by the Ziehl-Neelsen method. The entire lesion (or a good portion of it when the lesion was too large to handle) was then ground and homogenized in the least amount of physiologic saline with the aid of a sterile mortar and pestle, and was diluted further, if necessary, to enable passage through a 15- to 18-gauge needle. The homogenized material was divided into two equal parts. To one part was added an equal volume of sterile 10 per cent quartz powder,[15] and the mixture was inoculated subcutaneously into the right and left inguinal regions of 2 tuberculin-negative guinea pigs. If the amount of material was greater than 5 ml., the axillary regions were utilized as well. The remaining portion, without quartz, was similarly inoculated in its entirety into 2 other pigs. The animals were skin tested with 5 per cent Old Tuberculin (OT) at three weeks and twelve weeks, after which the survivors were sacrificed. The extent of gross tuberculous disease was recorded and all suspicious lesions were smeared, cultured, and subinoculated into normal guinea pigs.

Early in 1952, lesions were studied which had been removed from 6 different patients at Sunmount Veterans Administration Hospital. The patients had received prolonged antituberculous drug therapy (streptomycin, 1 gm., and para-aminosalicylic acid (PAS), 10 to 12 gm., daily) and had fulfilled the criteria for the so-called "target point."[16]

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[10] Steenken, W., Jr., and Gardner, L. U.: Am. Rev. Tubere., 1946, *54*, 51.

[11] Steenken, W., Jr.: Proc. Soc. Exper. Biol. & Med., 1935, *33*, 253.

[12] Vorwald, A. J., Dworski, M., and Pratt, P. C.: Am. Rev. Tubere., 1954, *69*, 841.

[13] Steenken, W., Jr.: Tr. Thirteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, Navy, St. Louis, Missouri, February, 1954, p. 302.

[14] Steele, J. D.: Discussion, Tr. Thirteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, Navy, St. Louis, Missouri, February, 1954, p. 305.

[15] Quartz suspension consisting of particles 1 to 3 microns in diameter, prepared as described above, was supplied by Mr. Morris Dworski of Saranac Laboratory, presently at Will Rogers Hospital.

[16] All cavities closed or filled in, stable roentgenograms for at least three months, and sputum negative for tubercle bacilli by culture for at least three months.

In June of 1953, the study was enlarged because of unpublished reports from the Saranac Laboratory. Forty-six lesions from 29 additional resections were obtained from patients who had received antituberculous drug therapy at Trudeau Sanatorium and Sunmount Veterans Administration Hospital. The specimens were handled exactly as already described except that an equal volume of sterile physiologic saline was added to the portion of the homogenate not mixed with quartz.

* * *

The guinea pigs inoculated with 5 of the first 6 specimens studied in 1952 remained free of tuberculous disease. From one lesion, however, the portion mixed with silica produced tuberculous disease in one animal and no disease in another animal; while the untreated portion failed to produce disease in either of 2 animals. These results are incorporated in the total experience which follows.

A total of 52 lesions obtained from 35 separate operations was studied. Of the *52* lesions, *39* were negative for the presence of viable tubercle bacilli by both methods (untreated and silica-treated), whereas *13* were positive for tubercle bacilli by either or both methods. A detailed analysis of the *13* positive lesions is presented in table 1.

As may be seen in table 1, of the *13* lesions which were positive for living tubercle bacilli, *8* were positive by both methods, *3* were positive only by the quartz method, and *2* were positive only by the non-quartz method. It is also interesting to observe that, although the lesions and their contents were thoroughly homogenized, *6* produced disease in all 4 animals, whereas 7 did not; and of these 7, *4* produced disease in only *one* of the *4* animals. Mate animals, whether or not they received the portion containing quartz, varied in their ability to acquire tuberculosis. There was no correlation between the bacilli count of the lesion and the degree of tuberculosis seen in the animals.

TABLE 1

ANALYSIS OF 13 POSITIVE SPECIMENS

Specimen Number	Type of Lesion	Gaffky Count	Degree of Gross Tuberculosis in Guinea Pigs*			
			With Quartz		Without Quartz	
			1	2	1	2
1	2 FIC, 1 and 1.5 cm., caseous	I to II	9.0	0	0	0
2	1.2 cm., FIC	00	2.0	0	0	0
3	Caseous, firm	00	12.0	0	0	0
4	CF	I	11.5	1.5	8.5	0
5	3 small FIC	IV	0	0	13.0	0
6	PL	II	0	0	3.5	2.5
7	PL	I to II	14.0	0	10.5	5.5
8	PL, caseous	II	3.5	4.5	13.0	7.5
9	1.5 cm. FIC necrotic	II	13.0	10	12.5	11.0
10	PL, necrotic	00	11.0	11.5	9.0	7.0
11	FIC, thin pus	II	13.0	12.5	11.0	12.5
12	1 cm. OC	II	10.0	1.5	1.5	5.0
13	2 cm. FIC, caseous	00	9.5	14.0	10.0	11.5

FIC—Filled-in cavity; OC—Open cavity; PL—Pooled lesions, small; CF—Conglomerate foci.

* Each organ (lungs, liver, spleen, lymph nodes) was assigned a value of 0 to 4 according to the amount of gross tuberculous disease; maximum total for each animal was therefore 16.

TABLE 2

RESULTS OF GUINEA PIG INOCULATION IN RELATION TO GAFFKY COUNT OF LESION

Gaffky	Number of Specimens	Results of Guinea Pig Inoculation	
		Negative	Positive
0	7	3	4
I to II	33	25	8
III to VII	12	11	1

It is obvious that none of the animals attained the maximum rating of 16 for their disease, not even the animals which had received quartz. The over-all degree of tuberculosis as observed at the end of three months, when all animals were sacrificed, was much less than would have been expected if the major population of the organisms seen on smears of the resected lesions had been viable and virulent. If that had been the case, many of the animals should have died of generalized tuberculosis prior to the sacrifice date, whereas actually only 2 animals died of tuberculosis.

The extent of disease in the animals which had received the quartz-treated portions was no greater than in those which had not. For the 8 specimens yielding at least 3 "positive" guinea pigs, the average degree of tuberculosis for the two groups was, respectively, 8.7 and 9.1.

In table 2 are related the results of guinea pig inoculations and the bacilli count of the lesions as demonstrated by the stained smear. Of the 12 lesions with Gaffky III (average of one bacillus in each field) or higher, only one was positive for tubercle bacilli on animal inoculation. The lesion produced disease in only one of the controls but in neither of the quartz-inoculated animals. The table shows that in this series of lesions there was no greater recovery of tubercle bacilli by animal inoculation from the lesions of high bacilli count than from those of low count. It must be borne in mind, however, that these figures are based on relatively few specimens and that the results could very well be different in a larger series.

In table 3 it will be noted that of the 40 "closed" lesions obtained from patients who met target point[16] criteria, 12.5 per cent were positive for tubercle bacilli by animal inoculation, whereas 70 per cent of the non-target point lesions were similarly positive. These figures substantiate previous results obtained by various groups in earlier studies on the recoverability of tubercle bacilli from resected lesions[17–20].

All of the animals which subsequently showed progressive disease (and some which did not) developed positive tuberculin skin tests. The intensity of the reaction was no more pronounced in the quartz- than in the non-quartz–inoculated animals. In some instances, the sensitivity waned, and in others it persisted undiminished until the sacrifice period.

[17] D'ESOPO, N., BERNSTEIN, S., DECKER, A. M., RALEIGH, J. W., AND STEENKEN, W., JR.: Tr. Twelfth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, Navy, Atlanta, Georgia, February, 1953, p. 229.

[18] STEELE, J. D.: Tr. Twelfth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, Navy, Atlanta, Georgia, February, 1953, p. 209.

[19] FALK, A., KAUFMAN, J. E., AND TUCKER, W. B.: Tr. Twelfth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, Navy, Atlanta, Georgia, February, 1953, p. 216.

[20] RALEIGH, J. W., MATHER, C. M., DECKER, A. M., AND BERNSTEIN, S.: Tr. Thirteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army, Navy, St. Louis, Missouri, February, 1954, p. 289.

TABLE 3

RESULTS OF GUINEA PIG INOCULATION RELATED TO ACHIEVEMENT OF "TARGET POINT" BY PATIENT

Target Point	Number of Specimens*	Guinea Pig Inoculation	
		Negative	Positive
Yes	40	35 (87.5%)	5 (12.5%)
No	10	3 (30.0%)	7 (70.0%)

* Sufficient data was not attainable to classify one patient from whom two lesions were obtained; hence the total of 50 instead of 52.

Those with persistent highly positive reactions always had demonstrable visceral disease which could be traced from the nodes draining the site of the inoculated area. The positive tuberculin tests in animals without demonstrable disease were attributed to the presence of many intact dead tubercle bacilli in the inoculated caseous material as well as to the tuberculoproteins from the organisms which had previously undergone autolysis. In fact, in some guinea pigs with no tuberculous disease, the local fibrocaseous silicotic lesions still had intact acid-fast organisms demonstrable in stained smear preparation. These bacilli were non-cultivatable, however, and when subinoculated into normal guinea pigs failed to produce local or progressive disease. This finding is not surprising, as it is well known that heat-killed tubercle bacilli have the ability to sensitize guinea pigs to OT. In unpublished experiments[21], the present writers have observed that guinea pigs inoculated with dead tubercle bacilli retained their skin sensitivity to OT, and smears made from the residual caseous lesions revealed many intact acid-fast organisms for at least twenty-seven months.

* * *

As it was found that tubercle bacilli could not be recovered by culture or animal inoculation from many lesions containing well-stained acid-fast bacilli by smear, the question arose concerning the adequacy of present-day techniques for recovering tubercle bacilli from such pathologic material. Culture and animal inoculation have always been considered the most sensitive methods for demonstrating tubercle bacilli in diagnostic material. In the past, these methods were resorted to only when repeated microscopy had failed to reveal acid-fast organisms or when there was a question of the identity of the organisms seen. Such techniques in the hands of competent and well-trained laboratory technicians have been responsible for the recovery of tubercle bacilli from approximately 25 per cent of patients with pulmonary disease of minimal extent, demonstrated roentgenographically, and with *repeatedly negative concentrated smears* of the sputum. This fair percentage of recovery was accomplished despite the fact that the small numbers of tubercle bacilli in the sputum were exposed to sodium hydroxide and sodium chloride (the latter the result of neutralization with N/1 hydrochloric acid) before being cultured on the same type of artificial medium used in the present study. One wonders, therefore, why these methods should be considered inadequate to recover the organisms from resected lung lesions which are not subjected to digestion and which commonly contain comparatively large numbers of stainable bacilli.

In the present study, special effort was made to eliminate procedures which have been shown to interfere with the recovery of tubercle bacilli and to add others which possibly could help in their recovery, namely:

(*1*) immediate processing of the specimen, (*2*) elimination of noninvolved tissue prior to homogenization, (*3*) use of the entire lesion or the major part thereof for inoculation, (*4*) use of 4 animals for each lesion studied, (*5*) elimination of the sodium hydroxide treatment of the specimen, and (*6*) inoculation of animals with the entire homogenate, usually in multiple sites, i.e., both axillary and inguinal regions.

A finding which might be misinterpreted by the inexperienced as well as the experienced investigator was an abscess-like lesion at the site of inoculation in many animals which received the quartz-treated specimen. Many times, acid-fast organisms could be found in these lesions by smear, the number depending upon the bacilli count of the original inoculated lesion. However, tubercle bacilli could not be recovered from them by culture or subinoculation into normal guinea pigs. Such lesions were never associated with caseation of the regional lymph nodes. The presence of stainable organisms in such lesions is not surprising, as it has been found that intact stainable tubercle bacilli, either heat-killed or living attenuated, can remain in a caseous abscess of guinea pigs for long periods of time.[21]

The finding of stainable but noncultivatable or disease-producing tubercle bacilli in residual necrotic lesions after prolonged chemotherapy has been duplicated in experimental tuberculosis of rabbits.[22] Material from one of these lesions, showing about 10 acid-fast bacilli per field, was inoculated intravenously into a normal rabbit as well as subcutaneously into guinea pigs without producing disease in either species.

The percentage of positive recoveries by any technique in a given series of resected tuberculous pulmonary lesions will depend a great deal on the type of lesion resected—from very high in a group of open cavities from patients who were discharging tubercle bacilli in the sputum to very low in a group of small closed lesions resected after maximum resolution and a long period with no tubercle bacilli in the sputum. For this reason, it is difficult to compare results from different institutions because no two of them would be likely to have a series composed of exactly the same type of lesions. It follows, then, that for the proper comparative evaluation of any new method (such as the one proposed by Hobby and associates[6,7]) for the recovery of bacilli from resected lesions, there must be a rigidly controlled study in which each specimen is divided into equal parts which are processed simultaneously, one by the new technique and the other by one of the older procedures.

In summary: The effect of silica on the recovery of tubercle bacilli from the resected lung lesions of patients who received prolonged antituberculous drug therapy was studied in 52 specimens from thirty-five operations.

The results indicated that the addition of silica to the lesion before guinea pig inoculation did not significantly increase the yield of positive recoveries over that obtained with the classical technique. Of the 13 positive lesions, 8 produced disease from both the quartz-added and control parts, 3 from the quartz-added part only, and 2 from the control part only. The incidence of positive recoveries appeared to be related to the clinical status of the patients. Tubercle bacilli were recovered from 5 of 40 lesions from patients who had achieved the so-called "target point," and from 7 of 10 lesions of those not meeting these criteria.

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August 17, 1954

[21] STEENKEN, W., JR., AND WOLINSKY, E.: Unpublished observations.
[22] STEENKEN, W., JR., AND WOLINSKY, E.: Nat. Tubere. A. Tr., 1954, p. 202.

Correspondence

PULMONARY TUBERCULOSIS DURING LONG-TERM SINGLE-DRUG (ISONIAZID) THERAPY

To the Editor of The American Review of Tuberculosis:

We think it necessary to draw attention to important misquotations of Medical Research Council findings in the report of Deuschle *et al.* on "The Course of Pulmonary Tuberculosis During Long-Term Single-Drug (Isoniazid) Therapy" (Am. Rev. Tuberc., 1954, *70*, 228), which have apparently led these authors to an incorrect conclusion. Their report states (p. 242) that, in the Medical Research Council trial of isoniazid, 2-plus and 3-plus radiographic improvement occurred in 26 per cent of patients on isoniazid alone, and in 29 per cent of patients on daily streptomycin plus isoniazid. In fact, 2-plus and 3-plus radiographic improvement was reported in 22 per cent of 120 patients on isoniazid alone compared with 38 per cent of 142 patients receiving daily streptomycin plus isoniazid (Medical Research Council, 1953*a*). In comment on these figures, the Medical Research Council report states that "this superiority of the [combined] treatment, which is apparent over the whole range of the X-ray assessment, is statistically highly significant" (i. e., at the 1 per cent level). It should be added that the report also shows that with the combined treatment there were substantial and statistically highly significant benefits at three months in the lowering of the sedimentation rate and in the suppression of tubercle bacilli in the sputum. The information from this Medical Research Council trial therefore indicates that a definite short-term enhancement of the effect of isoniazid alone is obtained by administering daily streptomycin in combination with isoniazid. These findings are clearly at variance with the statements of Deuschle *et al.* (presumably with the misquoted figures in mind) that "unfortunately this question of enhancement by the use of isoniazid-streptomycin . . . is one which probably cannot be convincingly answered by direct studies of the behavior of tuberculous lesions in patients" (p. 241); that "it has not been possible to establish with absolute certainty that isoniazid-streptomycin is superior to isoniazid alone" (p. 242); and that "the available evidence fails to show that isoniazid-streptomycin enjoys a substantial advantage over isoniazid alone . . . in terms of greater effectiveness during the early weeks of therapy" (p. 244).

We must also draw attention to the unsatisfactory way in which Deuschle *et al.* (p. 243) have compared the available results from two separate stages of the Medical Research Council trial (Medical Research Council, 1953*a*, 1953*b*, Brit. M. J., 1953, No. 4809, 521; No. 4844, 1005), in discussing the short-term efficacy of PAS plus isoniazid relative to that of isoniazid alone.

In the first place, they have not informed the reader, nor made any allowance for certain facts, namely:

(*a*) they have compared the results for patients treated with daily streptomycin plus isoniazid in the earlier stage of the trial with results in its later stage for a group of patients, some of whom were treated with streptomycin daily plus isoniazid, and some with streptomycin twice weekly plus isoniazid;

(*b*) young adults with acute bilateral disease were specifically excluded from the earlier report, but are included in the later report.

Moreover, as Deuschle *et al.* surmise, there was, as the trial progressed, a change in the

TABLE 1

M.R.C. Report	Treatment		Radiographic Changes: Number of Patients	Radiographic Changes: 2-Plus or 3-Plus Radiographic Improvement: Number	Radiographic Changes: 2-Plus or 3-Plus Radiographic Improvement: Per cent	Absence of Tubercle Bacilli at a Single Examination: Number of Patients Examined	Absence of Tubercle Bacilli at a Single Examination: Negative on Direct Examination and on Culture: Number	Absence of Tubercle Bacilli at a Single Examination: Negative on Direct Examination and on Culture: Per cent
Report 2. (1953*a*)	Isoniazid alone, 200 mg. daily	H	44	13	*30*	35	16	*46*
	Streptomycin, 1 gm. daily, plus isoniazid, 200 mg. daily	SH	56	28	*50*	43	31	*72*
Report 5. (1953*b*)	Streptomycin, 1 gm. daily, plus isoniazid, 200 mg. daily	SH	52	26	*50*	47	36	77
	PAS (sodium), 20 gm. daily, plus isoniazid, 200 mg. daily	20 PH	45	18	*40*	43	30	*70*

type of case admitted: "the proportion of patients admitted to the trial who were suffering from acute forms of the disease has been higher in recent months than in earlier stages" (Medical Research Council, 1953*b*).

Finally, the misquotations referred to earlier in this letter have been repeated, and the Medical Research Council figures for the isolation of tubercle bacilli in the later stage of the trial are also misquoted (p. 243).

In view of these differences between the stages of the Medical Research Council trial and the errors of misquotation, it is clear that no reliance can be placed on the comparison made by Deuschle *et al.*, nor indeed on the discussion which they base upon it. This is the more to be regretted since a comparison which takes account of the differences can readily be made from the published data for cases in disease group 2 (forms of pulmonary tuberculosis considered suitable for chemotherapy, other than acute rapidly progressive disease). The three-month results in terms of radiographic improvement and the suppression of tubercle bacilli in the sputum are summarized in table 1.

For this disease group, the three-month results with the combination daily streptomycin plus isoniazid in similar cases are in close accord for the two stages of the trial. The results with isoniazid alone, used in the earlier stage, may therefore be safely compared with those for PAS (sodium salt) plus isoniazid, used in the later stage. There is, it will be seen, some advantage to patients on PAS plus isoniazid, both in radiographic improvement and in the disappearance of tubercle bacilli from the sputum. We do not wish to suggest that this incomplete analysis yields conclusive evidence that PAS enhances the therapeutic effect of isoniazid. But the comparison is at least statistically valid, and so forms a more useful basis for discussion than that made by Deuschle *et al.*

Yours sincerely,

WALLACE FOX
IAN SUTHERLAND

TUBERCULOSIS AND STATISTICAL RESEARCH UNITS
MEDICAL RESEARCH COUNCIL
LONDON, ENGLAND

October 12, 1954

To the Editor of The American Review of Tuberculosis:

Drs. Fox and Sutherland have quite properly pointed out two errors which we made in citing Medical Research Council data in a recent paper on the use of isoniazid alone. Naturally, we regret the errors and are grateful to them for bringing them to our attention. On examination it appears, however, that the incorrect citations played no significant role in forming the particular conclusions which they have attacked, nor indeed any of the other conclusions of the article.

The incorrect citation which forms the basis for the first paragraph of the letter of Drs. Fox and Sutherland occurs in a footnote (p. 242). Inadvertently, values for streptomycin-PAS were cited as values for isoniazid-streptomycin but these values, as it happens, had not been used as evidence. The assumption made by Drs. Fox and Sutherland that we had these incorrectly cited values in mind when we made the various statements quoted in their letter is therefore unwarranted. Indeed, the context of the footnote was that we were *not* considering these particular data, which we considered to be not comparable with certain data from a U.S.P.H.S. study. The point is made by Drs. Fox and Sutherland that, had we considered the correct data (38 per cent substantial roentgenographic improvement with isoniazid-streptomycin as compared with 22 per cent with isoniazid alone), we should have concluded that "a definite short-term enhancement of the effect of isoniazid is obtained by administering daily streptomycin in combination with isoniazid." Though these values are undoubtedly statistically significant, a 16 per cent difference in trials of this nature is scarcely so impressive as to establish a superiority without question.

Although the quotations in their letter are drawn from separated places in our Discussion, they nevertheless correctly represent our present position on the matter and for the reasons presented in our article. We have not denied the possibility or even the probability that isoniazid with streptomycin may have some advantage over isoniazid alone, particularly in the early weeks of therapy. We have, indeed, cited evidence from studies other than those of the Medical Research Council which tend to show such an advantage. But we have not regarded the apparent advantage as securely established, nor do we believe that it is of such conspicuous degree as to make this combination the preferred treatment in all cases of tuberculosis.

The original error was carried over into our discussion (p. 243) of data derived from the M.R.C. studies relative to comparisons of isoniazid and isoniazid-PAS and was further compounded by a second incorrect citation relative to the values for the isolation of tubercle bacilli. Although the errors here, as in the first instance, are regretted, they concern matters of detail which again do not invalidate or importantly affect the principal arguments or conclusions.

Drs. Fox and Sutherland further take exception to what they consider the unsatisfactory way in which we compared results, from two separate stages of the M.R.C. trial, in analyzing the data concerning the relative efficacies of isoniazid and isoniazid-PAS. We ourselves emphasized that such indirect comparisons are unsatisfactory and were attempted *only because there has been no investigation in which these two regimens have been studied concurrently.* As we stated that differences in the results with isoniazid-streptomycin between the earlier and the later studies were presumably attributable to some differences in the type of cases treated, their objection that we did not inform the reader in detail of these and other minor differences is justified only in very small part.

In their letter, Drs. Fox and Sutherland have made a comparison relative to isoniazid and isoniazid-PAS, using subgroup data which we agree allow a more satisfactory

comparison. It is interesting that this comparison shows even less advantage in terms of substantial roentgenographic improvement (10 per cent) of isoniazid-PAS over isoniazid alone than we had concluded from our erroneous citation (13 per cent). The subgroup figures for the isolation of tubercle bacilli after three months of therapy also show less advantage for isoniazid-PAS than the figures we had incorrectly derived.

It is our position that, when two regimens for pulmonary tuberculosis both contain isoniazid, a difference in the results obtained on the two regimens must be quite marked to be meaningful. It is not the available statistical methods which are at fault, but the lack of sensitive techniques for the identification of pulmonary lesions of sufficient comparability to permit fine comparisons by the statisticians.

We have the greatest respect for the studies of the Tuberculosis Chemotherapy Trials Committee of the Medical Research Council. We agree that we have been justly taken to task by Drs. Fox and Sutherland for avoidable errors. At the same time we cannot agree with them that these relatively minor errors in scholarship in so exhaustive and detailed a consideration of the subject were of any real consequence, or that their correction necessitates revision of any important conclusions.

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November 12, 1954

To the Editor of The American Review of Tuberculosis:

We are grateful to you for an opportunity to see the reply of Deuschle *et al.* to our letter of October 12, and to make further comments.

The first part of our letter expressed the fear that the misquotations referred to might have led Deuschle *et al.* to an incorrect conclusion on the relative short-term merits of streptomycin plus isoniazid and isoniazid alone. In reply they state that they did not have the incorrectly cited values in mind when making the various statements quoted in our letter. In view of the indubitable relevance of the correct figures to those statements, we claim that they do require consideration, and that such consideration justifies conclusions differing importantly from those of Deuschle *et al.* We therefore summarize

the figures showing the progress after three months of all patients admitted concurrently to treatment, either with daily streptomycin plus isoniazid or with isoniazid alone, in the Medical Research Council trial (1953*a*):

	Treatment			
	Streptomycin, 1 Gm. Daily, Plus Isoniazid, 200 Mg. Daily		Isoniazid Alone, 200 Mg. Daily	
	Total Patients Available in Each Category	Per Cent Showing Stated Change	Total Patients Available in Each Category	Per Cent Showing Stated Change
Roentgenography: Improvement: 2-plus or 3-plus in three months	142	*58*	120	*22*
Sputum: Negative both on direct examination and on culture at three months	117	*67*	101	*37*
Temperature: Afebrile at three months (febrile at start)	88	*82*	59	*68*
Erythrocyte sedimentation rate: Fall to 0 to 10 from 21 or more, in three months	101	*45*	84	*25*

Taking these various measures of progress together, we consider that they demonstrate a short-term benefit to patients treated with daily streptomycin plus isoniazid which is substantially greater than that with isoniazid alone, and we believe that most clinicians will share this view. We wonder how much greater the difference between the results of two treatments would have to be for Deuschle *et al.* to regard it as clinically important.

The second part of our letter was more a criticism of methodology than a comment on the conclusions of Deuschle *et al.* on the relative short-term merits of PAS plus isoniazid and isoniazid alone. As shown in our letter, careful handling of the data already published permits a valid comparison of findings in two stages of the Medical Research Council trial. It is possible that Deuschle *et al.* might have drawn similar conclusions from our comparison as from their own, which they admit to be less satisfactory and also to contain inaccuracies. But this is irrelevant to our point and cannot be held to justify a comparison which is methodologically unsound.

Our position, based on the evidence in the Medical Research Council report (1953*a*), is therefore that a definite and substantial short-term enhancement of the effect of isoniazid is obtained by administering daily streptomycin with isoniazid. The relative short-term efficacy of PAS plus isoniazid and of isoniazid alone, we agree, has not yet been decided. It may be possible, in due course, to settle this by detailed comparisons of patients admitted to different stages of the large-scale trials, but only if these comparisons are made with care.

Yours sincerely,
WALLACE FOX
IAN SUTHERLAND

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November 30, 1954

DELAYED GROWTH OF MYCOBACTERIUM TUBERCULOSIS FROM RESECTED LUNG SPECIMENS

To the Editor of The American Review of Tuberculosis:

In view of recent interest which has been shown in delayed growth of *Mycobacterium tuberculosis* from resected lung specimens (Vandiviere, H. M., and Willis, H. S.: Tr. Twelfth Conference on Chemotherapy of Tuberculosis, Veterans Administration, Army, Navy, 1953, p. 201; Hobby, G. L., *et al.*: Am. Rev. Tuberc., 1954, *70*, 191), we would like to report several instances of late growth which have occurred in routine cultures at this hospital.

For the past several months, we have been incubating all cultures twelve weeks instead of the customary six weeks. In a group of 1,258 cultures on Löwenstein medium, there have been 23 cultures from different patients which showed no growth at six weeks but definite growth at twelve weeks. The 23 late growths represent an increase of 1.9 per cent for all cultures, or a 10 per cent increase in positive findings for tubercle bacilli.

The 23 late positive cultures represent 21 sputum specimens, one gastric washing, and one urine specimen. Concentrated smears of these sputum specimens showed 7 to be positive and 14 to be negative for acid-fast bacilli. There appeared to be no difference in distribution of late positive cultures due to race or sex.

It is interesting to note that all but 2 patients who yielded such cultures, one urine and one sputum specimen, were being treated with isoniazid. These 2 patients were receiving no drug therapy at the time. The 21 patients on isoniazid therapy were also receiving either PAS or streptomycin or a combination of these drugs.

In addition to the above, we have found 7 cultures from 3 patients whose sputum specimens were positive by smear but negative by culture until the fifth month of incubation, at which time all 7 cultures became positive. All 3 patients were receiving isoniazid.

The addition of isoniazid to the theraputic armamentarium has apparently caused a retardation of growth of the tubercle bacillus in cultures, and for this reason a re-assessment of the period of holding cultures seems advisable. Also, it might be recommended that cultures of sputum specimens which yield positive smears and negative cultures be held for an indefinite period, perhaps up to a year.

This information is being submitted in a preliminary report because of the widespread and pressing clinical problems that are raised. As more data accumulate, these observations will be further documented.

Sincerely yours,
A. Warren Jones
W. Harold Gentry

North Carolina Sanatorium
McCain, North Carolina

September 27, 1954

SOMATOTROPHIC HORMONE IN TUBERCULOSIS

To the Editor of The American Review of Tuberculosis:

Lately in this journal there appeared two articles[1, 2] which prompt us to jot down a few comments because the results described give the impression of being incompatible with our own observations. While preparing a lengthier report, in which our experiments will be detailed and those of other workers discussed, we would like to present at once some of our findings in order to clarify the situation.

[1] Youmans, G. P., and Youmans, A. S.: Am. Rev. Tuberc., 1954, *69*, 790.
[2] Bunn, P., and Robinson, F.: Am. Rev. Tuberc., 1954, *69*, 1016.

Youmans and Youmans[1] speak of a discrepancy between their results and ours. What they found, indeed among other facts, is that the somatotrophic hormone (STH) failed to prolong survival in mice bearing an *acute* tuberculous infection, whether receiving cortisone or not. What we had found and published[3, 4] is that: (*1*) STH markedly protected cortisone-maintained rats against experimental tuberculosis, diminishing the extent of lesions and the number of bacilli, as well as preventing catabolism and death; (*2*) STH protected mice against *chronic* tuberculous infection, in so far as the pulmonary lesions were reduced to less than half and the bacilli to approximately one-twenty-seventh of the control level. (There was practically no mortality in either group.)

Since then, we have further pursued our investigations, examining in particular the effect of STH treatment on *acute* tuberculous infection in mice. We performed several experiments, varying the strain of mice, strain and dose of bacilli, route of inoculation, dose of STH, et cetera. Although some decrease of pulmonary lesions and bacilli was noted, we never succeeded in showing any consistent prolongation of survival. Thinking this failure could be due to an endogenous secretion of cortisone-like hormone, induced by the disease itself or otherwise, we repeated the experiments in adrenalectomized mice, maintained with desoxycorticosterone or cortisone. Again we failed to find any significant protection by STH. Thus, our results are not discrepant but agree with those of Youmans and Youmans in that STH did not prolong survival in acutely infected mice.

Another point in which Youmans and Youmans' observations and ours are in accord is that we both failed to find a protection by STH against cortisone-induced "spontaneous" infections in mice, *when the two hormones are given at the same dose level*. They found a median survival time of 16 days in mice receiving 500 γ of cortisone per day and of 165 days in animals receiving 500 γ of cortisone and of STH per day. We found that the mortality reached 50 per cent on the seventeenth day in mice treated with 1 mg. of cortisone daily, whether receiving at the same time 1 mg. of STH daily or not. This also is not in contradiction with the results obtained by one of us in the rat[5] in which STH completely protected against cortisone-induced infections. It is just an example of the fact, which we have often noticed, that mice are less responsive than rats to the preparations of STH available at present and more sensitive to cortisone. (This may be gathered also from the work of Moon and co-workers[6].) In our experience, 200 and even 250 γ of STH per day do not suffice to stimulate growth in normal mice, whereas a proportional dose is effective in the rat.

More recently, Bunn and Robinson[2] failed to discover any protective influence of STH against ocular tuberculosis in the rabbit. Whereas ocular tuberculosis is a peculiar form of disease which may not be particularly suitable to demonstrate a favorable activity of STH, one may question whether these investigators did administer enough STH. They gave 300 γ per kg. per day to 3.3 kg. rabbits and did not obtain with such a dose any noteworthy effect on the weight of the animals and of the spleens in thirty days. If STH did not exert its primary growth-promoting and splenotrophic action, one cannot be surprised that it did not produce its other effects. The authors state that 10 γ of their product induced a growth of 1 gm. per day in hypophysectomized rats; it does not follow that 1 mg. will induce growth in an intact rabbit. Actually, their results could be used equally well to imply that growth hormone does not stimulate growth as to suggest that it cannot protect against tuberculosis in the rabbit. On the other hand, the weight of the

[3] Lemonde, P., *et al.*: J. Clin. Endocrinol. & Metab., 1952, *12*, 973.
[4] Lemonde, P., *et al.*: Ann. Endocrinol., 1952, *13*, 897.
[5] Selye, H.: Canad. M. A. J., 1951, *64*, 489.
[6] Moon, H. D., *et al.*: Cancer Research, 1952, *12*, 448.

spleen is not a very good index of STH activity in infected animals, since the hypertrophic effect of infection itself overshadows the STH effect and one does not know which effect is imputable to which cause, at least if there is no histologic examination of the organ. It appears that a set of uninfected controls would have been useful to ascertain STH action on body and spleen weight.

Since the publication of our positive results with STH against tuberculosis in cortisone-treated rats or in chronically infected mice, Lucherini and associates[7] performed similar experiments in guinea pigs and confirmed our findings: they obtained "a favourable influence of STH treatment, as the individual specific lesions turned out less severe and extensive than those showing at the same time in the controls"; 2 of 12 animals died during the sixty days of the experiment among the controls and none among the STH-treated guinea pigs.

Moreover, it has been reported[8] that STH has been used in several cases of human tuberculosis with encouraging results: increased body weight, sense of comfort and well-being (without euphoria or excitement, as with other drugs).

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October 4, 1954

FATAL CASE OF TUBERCULOSIS PRODUCED BY BCG

To the Editor of The American Review of Tuberculosis:

The description of Dr. Johannes Meyer in your journal of September, 1954, of a fatal case of tuberculosis produced by BCG vaccination is of the greatest importance, supported as it is by the scrupulously careful bacteriological investigations of Professor K. A. Jensen. The case raises some serious issues which have not previously been obvious, and the first is that the vaccine caused progressive tuberculosis in the child without having gained any increment in virulence. The 29 other children who were vaccinated from the same batch of BCG did not suffer any ill effect, and the tubercle bacilli from Dr. Meyer's patient were relatively harmless to guinea pigs. It follows, therefore, that BCG is capable of causing progressive tuberculosis within the limits of its attenuated virulence. It might be argued that a child who died from BCG vaccination would inevitably have succumbed sooner or later to natural tuberculous infection, since undue susceptibility to BCG would imply a grossly defective natural resistance. But it is well known that a virulent organism evokes a greater degree of acquired resistance than a less virulent one, and a person susceptible to BCG might well overcome a natural infection for that reason. A natural infection, moreover, would be inhaled or ingested and not injected in a large dose as in the process of vaccination. In the past, the theoretical danger of BCG has always been assumed to be that the attenuated organism might regain virulence, but we are now reminded that it can be dangerous without the slightest increase in virulence.

The second question arises out of Dr. Meyer's statement that this case alone should not discourage those who believe in the value of BCG vaccination. This, of course, is

[7] LUCHERINI, T., *et al.*: Policlinico, sez. med., 1953, *60*, 358.

[8] CARSTENSEN, B., PAULSEN, F., AND ROOS, I.: Scandinavian Tuberculosis Congress, Oslo, September, 1954.

perfectly true. There are few beneficial inoculations which have not occasionally been followed by tragic results, and accounts of deaths directly attributable to BCG are not common in the literature. Nevertheless, they are not unknown. Irvine[1] discusses an outbreak of tuberculosis with several deaths in 1930 in Ujpest in Hungary. Three of the 12 deaths which occurred in 562 vaccinated children were unquestionably due to tuberculosis and tuberculosis was suspected as the cause of the other 9 deaths. In the 3 cases which are discussed in detail, progressive disease followed shortly after vaccination, and in one of these cases the tubercle bacilli which were isolated were not pathogenic to guinea pigs. Irvine[1] also quotes the cases reported from Santiago by Ariztia, Orellano, and Del Rio in 1929, when 4 of 10 vaccinated children developed tuberculous lesions and one of them died of tuberculosis. More recently a death following vaccination was reported by Despierres and Viallier,[2] who describe how a newborn infant developed multiple cold abscesses ten weeks after vaccination. In Mexico,[3] deaths from tuberculosis following BCG vaccination caused anxiety until it was discovered that the BCG organism could not be proved to be responsible. Dr. Meyer states, however, that unless virulence tests on animals are carried out, "the BCG type cannot be distinguished from the human type" and, in fact, the tubercle bacilli from his patient were at first described as being human. There is good reason, therefore, to entertain the terrible suspicion that, in addition to the deaths which have been proved to have been due to BCG, there may have been many others which have been mistakenly attributed to superimposed infection with human tubercle bacilli.

If the indirect effects of BCG vaccination are included, the death roll rises steeply. It is not disputed that BCG creates hypersensitivity to tuberculin where it has not existed before and that, if a person is vaccinated who is incubating a tuberculous infection or who has previously been tuberculin-positive but has lost his skin hypersensitivity, the vaccination may precipitate serious tuberculous disease. Consequently, it is not surprising that Ustvedt[4] was able to find, from information which was not then complete, 21 cases of meningitis and miliary tuberculosis which had developed in vaccinated persons during the BCG campaign of the Joint Enterprise in Europe after the second World War. Wolk[5] describes a case of fatal hemorrhagic disease after BCG vaccination. Price[6] reports 4 deaths in persons "vaccinated but not immunized," in whom the disease began one to three months after vaccination. Dufourt and Despierres[7] discuss the case of an infant aged fourteen months who, eight days after vaccination, developed hilar adenitis and meningitis from which it died. A virulent, streptomycin-resistant tubercle bacillus was isolated from the child, but the authors were in no doubt that the vaccination was the precipitating factor in causing death. These cases have been found in a search of the literature which has been far from exhaustive.

If less serious tuberculous lesions are included, the casualties from BCG vaccination are greatly increased and the references in the literature too numerous to mention. Abscesses in regional lymph glands, erythema nodosum, mediastinal adenitis with atelectasis,

[1] Irvine, K. N.: B. C. G. Vaccination in Theory and Practice, Blackwell, Oxford, 1949.
[2] Despierres, G., and Viallier, J.: Rev. de la tubere., 1951, *15*, 451.
[3] Dominoo, P.: Rev. mex. de tubere., 1953, *14*, 129.
[4] Ustvedt, H. J.: Conference on European B. C. G. Programmes, Heinemann, London, 1951.
[5] Wolk, F.: Tuberculosearzt, 1952, *6*, 23.
[6] Price, D. S.: Irish J. M. Sc., 1954, *338*, 56.
[7] Dufourt, A., and Despierres, G.: Rev. de la tubere., 1951, *15*, 1111.

lupus vulgaris, irido-cyclitis resulting in loss of an eye, and intestinal obstruction have all been recorded as undoubted complications of vaccination.

It has always amazed me that the legend of the safety of BCG vaccination has so easily been established. Indeed, in the absence of conclusive proof of its efficacy, its alleged safety has become its strongest selling point, and many physicians use it in the belief that, if it does not do any good, at least it does not do any harm. I believe that BCG is the most dangerous substance which has ever taken shelter behind the principle of protective inoculation, and I can only suppose that its harmless reputation is based on the propagandists' axiom that, if a statement is repeated sufficiently often, it will eventually reach the status of truth. There is an urgent need for an impartial, expert inquiry into the dangers of BCG vaccination and, as there seems to be a more dispassionate attitude in the U.S.A. than in Europe to the vaccination, the task could most appropriately be entrusted to your own National Tuberculosis Association.

Yours sincerely,
E. F. James

Dungannon Chest Hospital
Dungannon
Co. Tyrone
Northern Ireland

November, 1954

Books

TUBERCULOSIS. British Medica' Bulletin, Vol. 10, No. 2., 1954. Edited by J. G. Scadding. Medical Department, The British Council, 65 Davies Street, London, 1954, Price, $2.75.

The present intensive attack on tuberculosis in all its phases is well illustrated by this collection of sixteen papers from Britain. *The British Medical Bulletin* might well be described as a "prestige" journal in which invited papers are published by the British Council, a government agency. This compilation is limited largely to the work within the purview of the Medical Research Council.

The epidemiology of the disease, first, in Europe, then locally as seen at the chest clinic and in industry, and also the detection of the disease by mass radiology make the first group of papers. The care of the tuberculous patient in industry reveals a lot of government planning but involves a degree of direction with which the American worker is unlikely to agree.

Special attention is naturally given to the elegant mass experiments in therapeutics being carried out by the M.R.C. by which so much has been discovered in a mere seven years. Prevention by vaccination with the vole bacillus has now passed from the laboratory to a planned clinical trial. The advantage claimed over BCG is that the vaccinating organism has a ceiling of virulence which prevents accidental gain in virulence. In a large population studied by Dr. Wells' group, the incidence of tuberculosis in the vaccinated was one-twenty-eighth of that in the controls.

Dr. Mackaness describes his interesting experiments on the survival and multiplication of virulent and nonvirulent tubercle bacilli in the monocytes of normal and immunized rabbits. Further experimental work on cortisone and surface-active polyoxyethylene ethers is described by Dr. R. J. W. Rees, and a paper is devoted to drug resistance.

Perhaps the most interesting section is that written by the clinicians, both medical and surgical. The surgeons can now apply the rules of excision and drainage under antimicrobial coverage and even carry out synoviectomy in bone and joint disease. Other articles deal with primary tuberculosis, artificial pneumothorax, and thoracic surgery. Dr. Honor Smith and Dr. J. G. Scadding, in their scholarly articles, discuss the diagnosis of tuberculous meningitis and the clinical use of antibacterial drugs. Clinical medicine has grown in stature and complexity, especially since 1935. Here we see it soundly based on scientific observation. While Dr. Scadding might be called somewhat dogmatic, his article is a good reference to give a colleague who wishes to know the present status of antituberculous therapy.

In summary, this is an excellent report on the progress which has been made in the tuberculosis field in the last one or two decades.

J. MACLEAN SMITH
New York, New York

PRINCIPLES AND PRACTICE OF ANTIBIOTIC THERAPY. By Henry Welch and others. Pp. 699, Medical Encyclopedia, New York, 1954, Price, $12.00.

An authoritative consolidation of historical, pharmacologic, commercial, and clinical facts about antibiotics is welcome. In this book, Dr. Welch and his collaborators have succeeded admirably in their attempt to review these aspects of antimicrobial therapy. The information is startlingly up-to-date, there being many references to journal articles

published in 1954. The first half of the book contains detailed descriptions of the drugs in common use as well as several rarer agents, such as subtilin and fumagillin, and a chapter on antibiotic synergism and antagonism with a note on "hormesis." Despite a tendency to present conflicting data without critical evaluation, this section is interesting and valuable. This reluctance to comment is particularly noticeable in the descriptions of the many dosage forms of each antibiotic. Perhaps it is simply admirable self-restraint (which this reviewer lacks) that keeps Dr. Welch from questioning the benefits to be derived from such products as penicillin toothpaste or troches. The reviewer would have appreciated a more detailed presentation of Eagle's experimental studies of penicillin's action rather than a brief mention of his results, and the omission of any reference to the important work of Umbreit on the mode of action of streptomycin is surprising.

In the second half of the book, the antibiotic treatment of specific infections is reviewed by several clinicians. In general, the material is excellent and up-to-date. As is perhaps unavoidable in such a series of chapters by different authors, some inconsistencies appear, but they are minor. The reviewer would take issue with some of the material. For example, the statement that Weil's disease is "the most widespread and important" infection produced by *Leptospira* is questionable. Furthermore, a somewhat unsatisfactory discussion of antibiotics in leptospirosis fails completely to mention the study of Hall *et al.* (Ann. Int. Med., 1951, *35*, 981), who tried antimicrobial agents in some 70 cases in Puerto Rico and not only observed no clinical benefit but made the important observation that antibiotics do not even shorten the period of leptospiremia in the disease. In the chapter summarizing antimicrobial therapy in pediatric practice, there is a striking tendency to garnish each regimen with extra sulfadiazine for good measure, a common pediatric procedure. However, the statement that sulfadiazine alone can be used for beta-hemolytic streptococcal infections of the respiratory tract is certainly unjustified in view of the clear superiority of penicillin or chlortetracycline in preventing rheumatic fever. Finally, although nine pages are devoted to the treatment of pinta and bejel, there is nowhere in the clinical section a description of the management of infections due to Friedländer's bacillus or to the *Bacteroides* group.

Despite these points and others which might be cavilled at, this book is a valuable collection of important facts about an important field.

Ivan L. Bennett, Jr.
Baltimore, Maryland

BOOKS RECEIVED

Year Book of Medicine. 1954–1955 Series. Edited by Paul B. Beeson, Carl Muschenheim, William B. Castle, Tinsley R. Harrison, Franz J. Ingelfinger, and Philip K. Bondy. Pp. 711, Year Book Publishers, Inc., Chicago, Illinois, 1954, Price, $6.00

XII Conference of the International Union Against Tuberculosis. Pp. 721, Union Internationale Contre La Tuberculose, 66, Boulevard Saint-Michel, Paris VI, France

My Life with the Microbes. By Selman A. Waksman. Pp. 364, Simon and Schuster, New York, 1954 Price, $5.00

Plombage in Pulmonary Tuberculosis. By Jens L. Hansen. Pp. 19, Munksgaard, Copenhagen, 1954, Price, $1.50

Hugh Roy Cullen. By Ed Kilman and Theon Wright. Pp. 376, Prentice-Hall, Inc., New York, 1954, Price, $4.00

Obituaries

JOHN ALEXANDER
1891–1954

In the death of Dr. John Alexander on July 16, 1954, medicine has lost one of the leading pioneers in thoracic surgery and more particularly in the surgical treatment of pulmonary tuberculosis. His writings and teachings parallel the rise of collapse and resectional therapy to a pinnacle which allowed surgical measures to be applied to a large percentage of patients with a minimum of mortality. In the preface to his original book,

John Alexander

The Surgery of Pulmonary Tuberculosis, the first to be written in the English language, Dr. Alexander expressed the belief that surgical methods would enable the saving of thousands of lives which would certainly be lost if this form of therapy was not undertaken. It can be said without exaggeration that his life was steadfastly dedicated to this purpose.

Dr. Alexander was particularly well known for his early adoption of a residency training program in thoracic surgery. This program, inaugurated in 1928, was augmented as early as 1932 to include the requirements which are essentially the same as those now required by the Board of Thoracic Surgery. It is definitely no overstatement to say that Dr. Alexander has trained more thoracic surgeons in this country than any other thoracic surgeon. A large number of them in turn have established residency programs of their own, with the result that the effect of his efforts in this direction are difficult to appreciate fully.

Dr. Alexander was born in Philadelphia on February 24, 1891, and was graduated from the University of Pennsylvania with the degrees of B.S. (1912), M.A., (1913), and M.D. (1916). He was a member of the varsity crew for four years and its captain during his last year in this activity. A glowing number of scholastic achievements accrued to him during his medical school career. Following an internship at the Pennsylvania Hospital, he enlisted with an American Unit in the French Army and later, with the entry of the United States into World War I, he transferred to the Medical Corps of the United States Army.

After the war he studied in Lyon with Leon Bérard, who at that time was employing surgery for patients with pulmonary tuberculosis. In recognition of his studies, he received a certificate in Surgery and Anatomy from the Université de Lyon in 1919.

For a year after his return to this country, Dr. Alexander served as assistant to the Professor of Clinical Surgery at the University of Pennsylvania. In 1920 he was called to the University of Michigan and was rapidly advanced to Assistant Professor of Surgery the following year. His tenure was soon interrupted by illness which took him to Saranac Lake, where lying upon a Bradford frame and in a plaster body cast, with his references held above him on a personally designed support, he compiled his first book on the surgical treatment of pulmonary tuberculosis. This volume was the first attempt to summarize the results of others in this new field and it immediately opened the eyes of phthisiologists in this country to the possibilities of the surgical treatment of pulmonary tuberculosis. For this publication, which appeared serially in the *American Journal of the Medical Sciences* in 1924 prior to its publication in book form, he received the Samuel D. Gross Prize of the Philadelphia Academy of Surgery in 1925.

Dr. Alexander returned to the University of Michigan in 1926. His interest in thoracic surgery continued, but it was not until two years later that his attention was almost exclusively devoted to this new specialty. At this time, in conjunction with Dr. John B. Barnwell, he surveyed the patients at the Michigan State Sanatorium and offered to this institution its first surgical program.

During this period Dr. Alexander applied the currently accepted measures in the treatment of pulmonary tuberculosis, and he developed two new procedures, namely, intercostal neurectomy and supraperiosteal, subcostal pneumonolysis with pectoral muscle filling. Although he used the latter operation only rarely, the principle of the technique is the same as that more recently applied to subcostal extraperiosteal plombage with Lucite® spheres. During the twenties it had been customary to remove eleven ribs, often in one stage, when performing a thoracoplasty. Dr. Alexander emphasized the advantage of staging the thoracoplasty into two operations and of resecting the upper ribs first. A rapid improvement in technique soon followed, and within the next several years he demonstrated the increased safety of removing fewer ribs at each stage, with the result that shortly thereafter it became customary to remove the upper seven ribs in not less than three stages. In the field of thoracoplasty he was also instrumental in popularizing anterior thoracoplasty and resection of the transverse processes of the vertebrae as aids in improving the thoracoplasty collapse.

In recognition of his attainments, Dr. Alexander became Professor of Surgery in 1932. A recurrence of illness in the same year served as a stimulus for beginning the rewriting and enlargement of his previous publication, which in 1937 evolved as a completely new book and the authoritative classic text on *The Collapse Therapy of Pulmonary Tuberculosis*. Dr. Alexander was early to recognize the advantages of resection in pulmonary tuberculosis, and in 1936 he performed his first resection, a pneumonectomy, for pulmonary tuberculosis with bronchostenosis. In more recent years, he was an ardent advocate of resection, but not to the exclusion of minor and major collapse therapy measures which he believed were of great advantage in the treatment of pulmonary tuberculosis. His interest in thoracic surgery included all aspects of this specialty, and among his contributions were the early use of the two-stage lobectomy technique for bronchiectasis, the recognition of the effectiveness of the resection of pulmonary metastases in certain instances, observations on the treatment of mediastinal and pulmonary neoplasms, and isolated studies in the field of cardiovascular diseases.

The well-deserved honors which have accrued to Dr. Alexander in recognition of his contributions to thoracic surgery are legion. In 1940 he received the honorary degree of Doctor of Science from the University of Pennsylvania. He was awarded the Trudeau Medal by the National Tuberculosis Association in 1941, and in the following year he was chosen to deliver the Trudeau Memorial Lecture at Saranac Lake. Recently he was recipient of the Bruce H. Douglas Award of the Michigan Trudeau Society. He was the only faculty member of the University of Michigan to have received both the Henry Russell Award and the Henry Russell Lectureship, these honors being conferred to a member of the faculty who has attained the highest distinction in the field of scholarship. Dr. Alexander was a past president of the American Association for Thoracic Surgery, president-elect of the American Trudeau Society, an office which he had to relinquish because of recurrence of illness in 1946, a director and vice-president of the National Tuberculosis Association, and a past president of the Michigan Tuberculosis Association. He was a founder member of the American Board of Surgery and the Board of Thoracic Surgery. He was a member of the Editorial Boards of the *Journal of Thoracic Surgery*, the *International Abstract of Surgery*, and between 1938 and 1946 he served on the Editorial Board of this journal.

Dr. Alexander was a Fellow of the American College of Surgeons and a member of the American Surgical Association, Central Surgical Association, Société Internationale de Chirurgie, Society for Clinical Surrery, American Medical Association, and the Michigan State Medical Society. He was an honorary member of the Society of Thoracic Surgery of Great Britain and Ireland, Detroit Academy of Surgery, Sociedad de Argentina de Cirurjanos, Société Belge de Chirurgie, Société Francaise de la Tuberculose, Sociedad Paraguaya de Tisiologia, and the Sociedad Ecutoriana de Tisiologia. He was also a member of Alpha Omega Alpha, Sigma Xi, Phi Kappa Phi, Alpha Mu Pi Omega, Delta Tau Delta, and an honorary member of Nu Sigma Nu. At the time of his death, Dr. Alexander was Thoracic Surgeon to the Michigan State Sanatorium, the Jackson County Sanatorium, and the Genessee County Tuberculosis Sanatorium. He was a member of the Committee of Civilian Consultants to the Surgeon-General of the United States Navy, and he had formerly been a consultant on the Committee on Thoracic Surgery of the National Research Council and the Medical Advisory Committee of the Medical Council of the Veterans Administration.

Surviving are his wife, the former Emma Ward Woolfolk, two sisters, Mrs. William T. Campbell and Mrs. Thomas R. Peirsol, Jr., and a brother, Stirling C. Alexander.

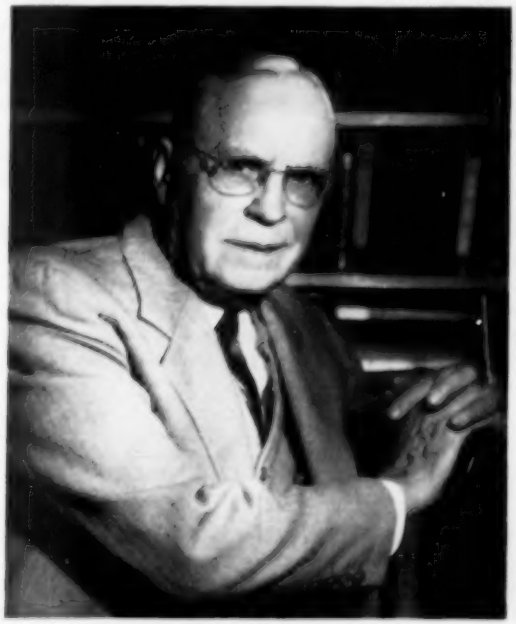
Dr. Alexander possessed an unusual warmth and charm of personality. His courage

and determination in the face of apparently insurmountable obstacles, his inspiration to others who had contracted tuberculosis or other protracted illnesses, his continued cheerfulness and optimism and complete absence of complaint in the face of physical handicaps are characteristics which have endeared him to the medical profession and his many friends and admirers who have repeatedly described him as a truly remarkable person. As a pioneer in thoracic surgery and a crusader in the treatment of pulmonary tuberculosis, his accomplishments will be recorded in the annals of medical history.

C. H.

LEWIS JEFFERSON MOORMAN
1875–1954

Dr. Lewis Jefferson Moorman, former president of the American Trudeau Society and of the National Tuberculosis Association, died in Oklahoma City on August 2, 1954, at the age of seventy-nine. Dr. Moorman enjoyed a long and distinguished career in medicine. He was born in Leitchfield, Kentucky, on February 9, 1875. He graduated from the Hospital College of Medicine, Louisville, Kentucky, in 1901. After a short trial at practice in Alabama, he, with a fellow graduate, went west and opened an office in the prairie town of Jet, which was then in Indian Territory. Those were the days of the rush to stake out claims in nearby opened government lands. Thousands of people crowded the small towns along the border of the land grants. Here Dr. Moorman had wide and varied experiences serving the frontiers men and the Indians who wandered the plains. His interest in the problems arising from tuberculosis among the Indians led him to give



Lewis Jefferson Moorman

much time during his life to help solve the difficulties of control and treatment. In 1948, Dr. Moorman was made chairman of a committee chosen by the U. S. Department of the Interior to study health conditions among the Navajo and Hopi Indians.

In 1907, Dr. Moorman, feeling that a metropolitan practice would be more to his liking, moved to Oklahoma City. Two years later he pursued a postgraduate course in Vienna, at that time the center of European medical teaching. Upon his return home he soon became a leader in the medical fraternity in city and state. He was especially interested in diseases of the chest, in which specialty he spent much of his life's work. For many years he was Director of the Oklahoma Cottage Sanatorium, and he was the Founder and Director of the Moorman Farm Sanatorium.

In 1909, Dr. Moorman married Mary Davis Christian, a niece of Dr. Henry A. Christian. Three children were born to them.

Dr. Moorman's high professional attainments gained him many positions of responsibility and honor. He was Professor of Clinical Medicine at the University of Oklahoma (1922–1935), and Dean of the Medical School from 1931 to 1935. From 1948 he was Professor Emeritus and Lecturer in the history of Medicine and Medical Ethics. He was, for many years, secretary-treasurer of the Oklahoma State Medical Society (President 1919–1920 and Honorary President for life), and Editor of the state medical journal. He became president of many of the professional societies of which he was a member. These included the Southern Medical Association; the County Medical Society; the Oklahoma City Academy of Medicine; the American Trudeau Society (1941–1942) and the National Tuberculosis Association (1943–1944); and the Oklahoma Public Health Association. He was president for thirty years of the Oklahoma City Tuberculosis Society.

From 1938 to 1948, he served as a member of the Editorial Board of this journal.

Dr. Moorman was a Fellow of the American College of Physicians and at one time Vice President of the American Clinical and Climatological Association; honorary member of the staff of St. Anthony Hospital; and affiliated with the University, Wesley, and Mercy Hospitals; and formerly, Medical Superintendent of the State University Hospital and Crippled Children Hospital.

Dr. Moorman was interested in the history of Medicine and published a volume on *Tuberculosis and Genius*, in which he traced the lives of many of the great in history who had tuberculosis. His autobiography, *Pioneer Doctor*, appeared in 1951. In this volume, among other things, are found many stories of early days in the plains and reflections on the art and practice of medicine.

As Dr. Christian said of Dr. Moorman in his foreword to *Pioneer Doctor*, "he had the pioneer spirit, the love of the patient, an innate true religion, a broad knowledge of medical lore and an appreciation of the best in the literature of the English language."

A host of patients and friends will miss this good physician of gentle manner, soft voice, and delightful humor.

E. N.

CAMERON ST. CLAIR GUILD
1896–1954

Cameron St. Clair Guild, the first Executive Secretary of the American Trudeau Society, died suddenly on October 18, 1954, at Sunmount, New York, where he was Chief of Professional Services in the Veterans Administration Hospital. His death brought to an untimely end a career influential in the development of public health and of tuberculosis control during the past quarter of a century.

Dr. Guild, "Cam" to his close friends, was born in Mosquodoboit Harbor near Halifax, Nova Scotia, on September 17, 1896. Educated in public schools, he served in the First World War as a Lieutenant in the Royal Flying Corps. Before studying medicine at Dalhousie University, where he received his M.D. and C.M. degrees in 1925, he taught school and worked as a surveyor. After graduation in medicine he was sent by the International Health Board of the Rockefeller Foundation to the South for training; and in 1926 he became Health Officer of Lee County, Mississippi, where a model county health unit was set up in Tupelo. After four years and when the county health unit was well established, he returned east to Yale School of Public Health, where he received the degree of Doctor of Public Health in June, 1931. During the same year he served as Associate Field Director of the American Public Health Association. He then worked for a year as a member of the Research Staff of the Committee on the Cost of Medical Care.

With this experience, training, and demonstrated willingness to fight for the underdog, he joined the staff of the National Tuberculosis Association on June 1, 1932, as Field Secretary for the study of tuberculosis among Negroes. In 1937 an authoritative report of the Committee on Tuberculosis Among Negroes, of which he was then the Secretary, was published. Dr. Guild continued to devote a considerable part of his time to this problem as Director of the Negro Program of the National Tuberculosis Association. In 1943 he was also given the direction of the campaign against tuberculosis among Spanish-speaking people in the United States of America.

By the end of 1940 the growing American Trudeau Society, reorganized from the American Sanatorium Association in 1939, needed an Executive Secretary. Dr. Guild was appointed part-time Executive Secretary on January 1, 1941. Under his agressive and enthusiastic direction, the American Trudeau Society grew from six or seven hundred to more than three thousand members, with twenty-one active committees. He started the News Letter and many of the present features of the Society. He resigned in May, 1947, to answer what he considered a greater challenge by joining the Medical Department of the Veterans Administration as Branch Chief of Tuberculosis in the New York Area. His later transfer to Sunmount as Chief of Professional Services placed him where he could accomplish much through the pioneer work on antimicrobial and surgical therapy done at that Veterans Administration Hospital and through the organization of the annual Sunmount Therapy Conferences.

At heart, Dr. Guild was always a fighting crusader. He fought for better health for the farmers of Mississippi; he fought for better and less expensive medical care for the middle class; he fought against tuberculosis and ignorance among Negroes and Mexican-Americans; he fought to organize the medical section of the National Tuberculosis Association on a wider basis; he went out still fighting for better care of tuberculous veterans.

J. L. W.

NOTICES

HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH ANNOUNCES PUBLIC HEALTH SCHOLARSHIPS

Scholarships for the Academic Year 1955–1956 will be granted to individuals of high professional promise in awards ranging from part tuition to tuition plus a stipend, according to the qualifications and financial needs of the applicants. The Scholarships Funds are limited and are primarily intended for citizens of the United States.

Scholarship applicants must be eligible for admission to the School as a candidate for one of the following degrees: Master of Public Health, Doctor of Public Health, Master of Science in Hygiene, Doctor of Science in Hygiene, Master of Industrial Health.

Scholarships are available to those in the following categories who wish to obtain postgraduate education in the field of public health or in one of the basic sciences related to public health:

1. Physicians, dentists, and veterinarians
2. Industrial physicians
3. Public health nurses with a college degree and satisfactory field experience
4. Social workers with a master's degree from an approved school of social work and acceptable experience in the field of medical or psychiatric social work
5. Health educators with the following background: college degree, training in either health education or the natural and social sciences; experience in general education or community health work
6. College graduates who have concentrated in one of the natural sciences or engineering (environmental aspects)

A catalogue of the school, admission and scholarship applications, and further information may be obtained by writing to the Secretary, Harvard School of Public Health, 55 Shattuck Street, Boston 15, Massachusetts.

Scholarship applicants must return completed admission and scholarship applications to the Harvard School of Public Health by March 1, 1955.

ILLINOIS TUBERCULOSIS ASSOCIATION GRANTS FOR TUBERCULOSIS RESEARCH

Grants for tuberculosis research recently were made available by the Illinois Tuberculosis Association under a newly established program designed to stimulate medical research in this field in Illinois.

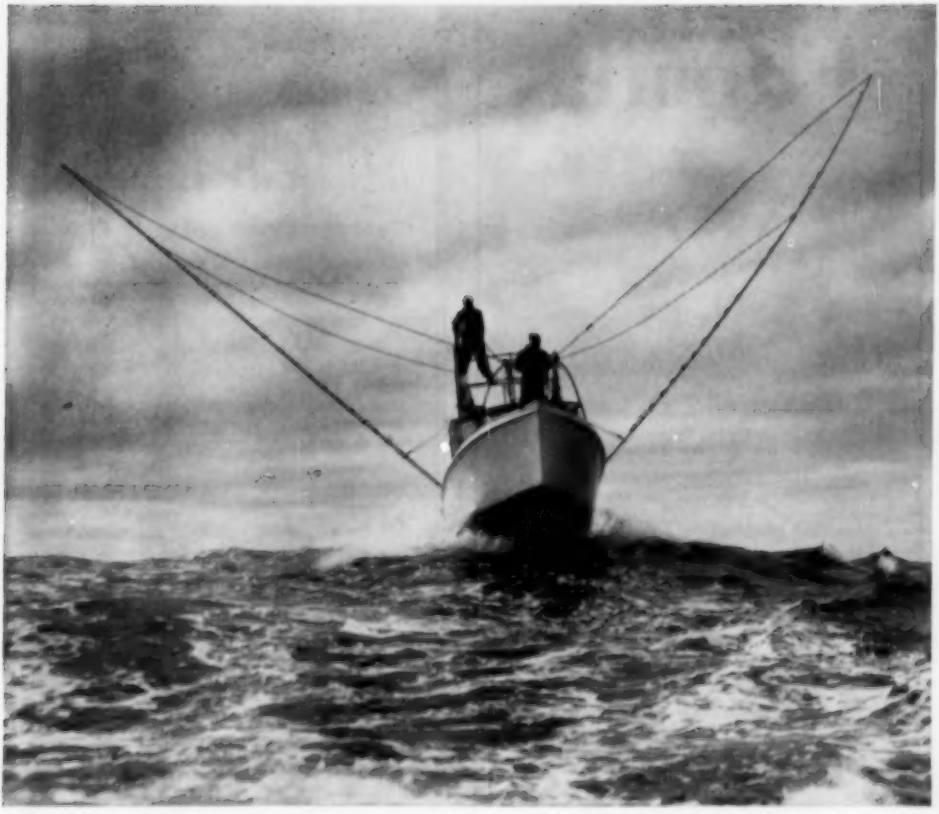
Applications submitted prior to the January 15 deadline soon will be reviewed by the research committee, which is serving as a screening group in considering and recommending approval of grants.

The next deadline for applications for grants has been set for June 1, 1955. They should be submitted to Robert H. Ebert, M.D., research committee chairman, Illinois Tuberculosis Association, 730 South Sixth Street, Springfield, Illinois.

Prospective projects should be connected with tuberculosis. Preference in awarding grants will be given to qualified schools and institutions in Illinois which are equipped with adequate facilities. The size and number of grants will be determined by the research committee.

Applications for grants must include the following: general statement of the problem; name of the principal investigator and a biographical sketch with complete list of publications; description of facilities where research will be conducted; and the amount of money requested.

Additional information as well as a list of research projects currently being sponsored by the National Tuberculosis Association and the American Trudeau Society may be obtained from Ben D. Kiningham, Jr., executive director, Illinois Tuberculosis Association, 730 South Sixth Street, Springfield, Illinois.



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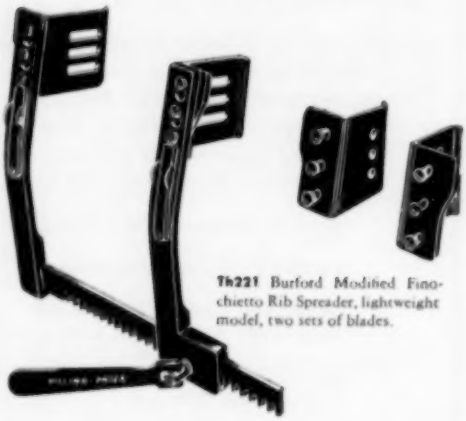

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[1] *Smith, C. R.: Disinfectants for tuberculosis hygiene, Soap and Sanitary Chemicals 27:120 (Sept.) 1951; 27:143 (Oct.) 1951.*

[2] *Klarmann, E. G.; Wright, E. S. and Shternov, V. A.: Prolongation of the antibacterial potential of disinfected surfaces, Applied Microbiology 1:19 (Jan.) 1953.*

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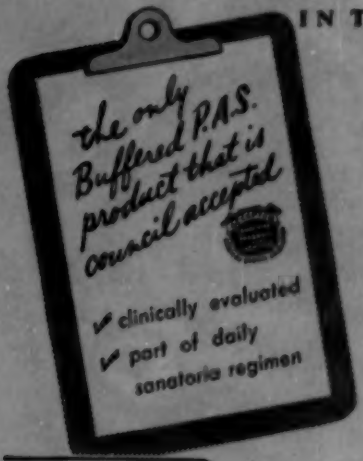

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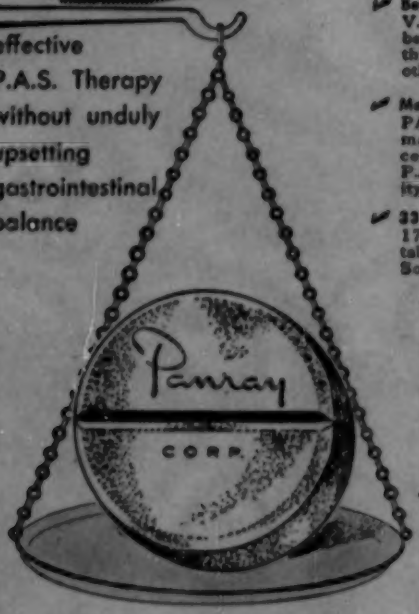

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References

(1) V.A. Quarterly Prog. Report, April '53

(2) V.A. Quarterly Prog. Report, Oct. '54

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